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DIABETIC ACIDOSIS AND COMA*

FRANK N ALLAN

Coma was formerly the cause of death of most patients suffering from diabetes, the condition was hopeless until the discovery of insulin Although the danger of death from diabetic coma can now be almost entirely eliminated, there are nevertheless still many fatalities According to reports of the Metropolitan Life Insurance Company in 1930, coma occurred in 37 per cent of fatal cases of diabetes Every diabetic patient should be prepared to guard against this dangerous complication and it is also important for physicians to be prepared to deal with it promptly and effectively should it occur

CAUSE

Diabetic coma is due to acidosis or acid poisoning, resulting from the formation of poisonous acids in the body when diabetes becomes severe and is uncontrolled Sometimes it occurs before the existence of diabetes has been discovered Its prevention under these circumstances depends on education of the public to seek medical advice at the first signs of ill health More often, acidosis occurs in cases of known diabetes, either because of inadequate treatment, or because something happens to aggravate the condition, or to interrupt the usual treatment In such cases prevention depends on institution of thorough treatment and continuous supervision

* Read at the meeting of the Austin Flint Medical Society Algona Iowa, October 6 1931

Acidosis may develop under various conditions If treatment of severe diabetes is neglected, there may be immediate danger Interruption of treatment with insulin in cases in which large doses have been required regularly may lead quickly to acidosis The effects of neglect of diet may be less sudden but may become equally serious Acidosis is, of course, much more likely to occur in a case of severe diabetes, but it must be remembered that mild diabetes may become severe with excessive and prolonged overeating Even more rapid and more serious aggravation of diabetes may result from occurrence of complications Infections are particularly serious Hyperthyroidism is less common, but a dangerous complication Surgical operations have the same effect Even a simple operation in a case of previously mild diabetes may be potentially dangerous A nervous shock or an accident may cause a striking change in diabetes It should be emphasized that even in cases of mild diabetes serious acidosis may develop, when the condition is altered by these various circumstances

SYMPTOMS AND SIGNS

Development of the symptoms of acidosis depends to some extent on the duration of the disorder and the rapidity with which it occurs If it comes on slowly, the cardinal symptoms of diabetes become evident first, or if they are already present they become aggravated There is loss of strength, frequent excessive urination, and increased thirst The symptoms of toxemia follow If, however, acidosis develops suddenly because of an abrupt change in diabetes, the symptoms of toxemia may occur immediately The first symptoms are loss of appetite, nausea, vomiting, and pains and aches in various parts of the body There may be dull headache or backache and mild, cramping pains in the extremities, or there may be intense, agonizing pain occurring particularly in the abdomen and thorax These symptoms are accompanied or followed by increasing prostration Drowsiness develops, then stupor, and finally complete unconsciousness Coma almost never appears without warning signs The patient feels ill a few hours at least or

perhaps a few days before going into coma Yet the warning may be easily overlooked Although the patient may feel ill his appearance may be deceptive at the beginning The flushed cheeks may give an erroneous impression of good health The symptoms may be attributed to some simple disturbance The patient may think that he is ill because he has eaten something that has disagreed with him, or he may think that he is getting the "flu" A description of the symptoms given to a physician over the telephone may not excite suspicion of the serious nature of the trouble

When the physician sees the patient, however, he will recognize at once definite signs Acidosis presents characteristic features The odor of acetone on the breath may be noted by the physician as he comes into the patient's room Evidence of dehydration of the skin, and a parched tongue can be seen at a glance Decrease of ocular tension can be noted by palpation of the eyeballs Shortness of breath may be apparent, and if the patient is comatose, or on the border of coma the deep, labored breathing is unmistakable. The coma of diabetic acidosis is accompanied by three characteristic changes dehydration, stimulation of respiration, and circulatory changes The cheeks are usually flushed and the lips are red The difficulty of breathing in the absence of cyanosis of the face and lips attracts attention The extremities become cold and may be bluish and mottled The heart beat is rapid, there may be a terminal fall in blood pressure

LABORATORY TESTS

The clinical signs may indicate the diagnosis clearly but laboratory tests verify it Tests of the urine show the presence of sugar and acetone bodies. Glycosuria and acetonuria are almost never absent, but may be absent under two rare circumstances treatment with insulin, prior to examination, may have checked glycosuria, or advanced failure of renal function may have resulted in cessation of excretion of the acetone bodies. The presence of acetone bodies in the plasma and serum, however, can be demonstrated by the nitroprusside test Simpler and more sensitive than the tests for acetonuria or acetonemia

is the test for acetone in the breath A drop of Scott-Wilson reagent placed on a glass slide and held before the patient's mouth or nostrils will turn milky, and in a moment will indicate ketosis

The diagnosis of diabetic acidosis or coma is not likely to be mistaken if the clinical signs described are present, and if the tests for glycosuria and ketosis are positive Further laboratory investigation, however, yields valuable information in determining the seriousness of the condition and in guiding treatment The test of the carbon dioxide combining power of the blood plasma is most important The value for carbon dioxide is normally from 55 to 70 volumes per cent A value for carbon dioxide from 40 to 50 indicates mild acidosis, usually without symptoms When the value for carbon dioxide falls below 40, symptoms appear and the patient complains of weakness and malaise When it is below 30 there is prostration, shortness of breath, gastro-intestinal disturbance, and aches and pains A value for carbon dioxide less than 20 indicates severe acidosis, there is extreme prostration and usually loss of consciousness, and air hunger There is need for immediate intensive treatment The danger is not passed until the value for carbon dioxide has returned to more than 30 The concentration of blood sugar is always elevated before treatment of acidosis is begun, but the value for blood sugar does not indicate the seriousness of the condition A patient may be in coma with a reading for blood sugar only slightly more than 200 mg in each 100 c c. On the other hand, the value for blood sugar may be more than 500 without ketosis However, tests of blood sugar help to guide treatment

Mention must be made of two laboratory findings which often cause confusion in examination in cases of acidosis It is common to find albumin and casts in the urine This is due to injury to the kidney resulting from the toxemia It may, however, lead to the idea that there is primary disease of the kidney Leukocytosis, which is commonly found in cases of acidosis, may likewise suggest other complications, if it is found in a case in which there is abdominal pain, nausea, and vomiting, it may be

difficult to exclude the possibility of appendicitis Both albuminuria and leukocytosis disappear promptly with treatment of diabetes Another laboratory finding is the lipemia frequently seen in cases of acidosis The peculiar color of the blood may be apparent when a specimen is withdrawn for examination, and when it is permitted to stand, a creamy layer may appear at the top Chemical determination of the concentration of fat in the blood may show it to be increased more than ten times normal

DIFFERENTIAL DIAGNOSIS

From a consideration of these various clinical and laboratory features of acidosis it would appear that the diagnosis is simple, yet, errors are made either because the possibility of acidosis is not considered, or because some complicating illness is wrongly thought to be acidosis Acidosis should be thought of whenever a patient with diabetes becomes acutely ill, and the urine should be tested at once If it is free from sugar, or if it contains only a trace, the suspicion of acidosis may be dismissed If it contains sugar and diacetic acid, the other signs of acidosis should be verified The history taking and the general examination should be thorough Careful search should be made for complications which may be responsible for the onset of acidosis, or which may contribute to the picture of the patient's illness

Special attention must be given to two problems in differential diagnosis If the patient is in a precomatose state, the abdominal pain and vomiting suggest intra-abdominal disease The simulation of appendicitis by acidosis has already been mentioned The possibility that appendicitis and acidosis may occur coincidently must also be kept in mind If the patient is comatose, the various factors must be considered that may cause loss of consciousness of persons who do not have diabetes Also hypoglycemia from overtreatment with insulin must be kept in mind The points which should guide one to the correct diagnosis of diabetic coma are, the history of the onset, the appearance of the patient, the odor of acetone, the tests for sugar and acetone bodies, and finally the carbon dioxide combining power of the blood plasma The history alone should be

a reliable guide As emphasized before, diabetic coma almost never develops without warning signs, and attention to this rule will avoid confusion

Ketosis may occur if patients do not have diabetes in the course of starvation, fever, and gastro-intestinal disturbances Yet the amount of ketone bodies formed is usually so small that there is no change in acid base equilibrium In the case of a sick child, however, hyperpnea and an odor of acetone on the breath may simulate the clinical picture of acidosis, and may give rise to errors of diagnosis The test of the urine for sugar is the deciding point Absence of glycosuria shows that the ketosis is not due to diabetes On the other hand, even glycosuria may be present because of a low renal threshold, and ketosis which occurs with renal glycosuria in the course of starvation may be intensified by infections and after surgical operations, as pointed out by Allan and Vanzant Under such circumstances, determination of the blood sugar is essential for diagnosis

TREATMENT

Successful treatment of diabetic acidosis depends on consideration of various factors, but by far the most important factor is insulin In diabetic acidosis there are three disturbances to be overcome, toxemia from the presence of acetone bodies, disturbance of the acid base equilibrium, and dehydration Insulin overcomes or helps to overcome each one of these disturbances Insulin brings about combustion of the acetone bodies and checks their formation, the base which has been combined with them is liberated, and consequently there is automatic restoration of the acid base equilibrium, the glycosuria is checked and the diuresis responsible for dehydration is abolished The most important factors in treatment of acidosis are to give insulin, to give it early, and to give it in adequate dosage

The size of the initial dose which should be given depends on various factors such as the clinical condition of the patient, the value for blood sugar, the age and weight, and the duration of acidosis It is difficult to lay down any definite rule However, any adult patient who is in a state of acidosis may be

given 20 to 30 units of insulin at once, if the patient is comatose, 40 to 60 units may be used, if the condition appears critical, 80 to 120 units should be given without delay If there is extreme prostration, with circulatory failure, so that the pulse cannot be felt, it is advisable to give at least part of the first dose intravenously, the remainder may be given subcutaneously A child aged less than six years may be given a fourth of the dosage recommended for adults and a child less than fourteen, half of this dosage

The size of the subsequent doses, and the intervals between the injections, should depend on the clinical progress of the patient and the height and rate of fall of the blood sugar At least 10 to 20 units may be given to an adult every four hours, until the value for blood sugar is down to 200 mg for each 100 c c, or until glycosuria has been reduced to a trace This dosage may be repeated every one to two hours if the patient is slow in responding to treatment, or if the value for blood sugar remains more than 300 If examination of blood sugar is not available the treatment may be guided by frequent examination of the urine, but it must be kept in mind that the urine may be slow in reflecting the change which takes place in the blood sugar

Next in importance to administration of insulin is administration of fluid to overcome the dehydration At least 3,000 c c. of fluid should be given in twenty four hours If the patient can take fluids by mouth he may be given a glass of water or its equivalent every hour for the first six hours Tea, coffee, broth, orange juice, ginger ale, and hot lemonade may be used If the patient has been nauseated or is vomiting, oral administration of fluids should not be attempted for four or five hours Physiologic solution of sodium chloride should then be given subcutaneously or intravenously Fluid may also be given by proctoclysis

Nourishment is the next point which must receive attention, 100 to 150 gm of glucose, or its equivalent, should be given during the first twenty four hours If the patient can tolerate food by mouth a soft diet may be prescribed containing cereal, bread, milk, eggs, and fruit juices If the patient is nauseated

or if he is in coma, the glucose must be given intravenously, 50 gm of glucose in 5 or 10 per cent solution may be injected two or three times It may seem irrational to inject glucose intravenously when the blood sugar is high, yet, hyperglycemia can do no harm, and although a part of the glucose injected may be excreted, enough may be utilized to be of value Furthermore, an increased amount of glucose given with insulin may cause the disappearance of acetone bodies more rapidly My studies of the glucose equivalent of insulin in depancreatized dogs showed that each unit of insulin would provide for the utilization of a larger amount of glucose if the supply of glucose were large However, there is no reason for haste in administration of glucose, and it is just as well to wait until the blood sugar has begun to fall before giving it As soon as it can be tolerated, a diet with 100 gm of carbohydrate, 50 to 60 gm of protein, and enough fat to provide 10 per cent more than the basal calorie requirement, may be prescribed

Recovery from coma usually occurs if insulin is given in suitable dosage, but in certain cases recovery may be hastened and the risk reduced by administration of alkali If acidosis is prolonged the heart and kidneys may be seriously injured, and this risk cannot be ignored There are certain cases of coma in which the carbon dioxide combining power remains low for many hours after disappearance of acetone bodies from the urine and blood In such cases there is no danger from administration of alkali in small dosage and considerable benefit may be derived Experience indicates that the use of sodium bicarbonate is wise in any case of complete coma, 10 or 15 gm may be given by stomach tube after gastric lavage If there is delay in regaining consciousness, or if the carbon dioxide combining power remains below 20, administration of more alkali may be considered, but a total of 30 gm is rarely needed If it is decided to use more alkali 3 gm of sodium bicarbonate dissolved in half a glass of warm water may be given by mouth or by stomach tube every three hours If the patient's condition seems critical, sodium bicarbonate given intravenously may bring about rapid improvement One may employ 300 to 500 c c of a 5 per cent solution

The use of alkali has been a debated problem Some authorities advise against its use because there may be recovery without it and because harm was done by the intensive use of alkali as formerly practiced, but the best policy in this, as in many other debated problems, would seem to be to avoid extremes The use of alkali in reasonable dosage in suitable cases may be of value and can do no harm

Circulatory failure is one of the most serious problems in diabetic coma, and attention must be directed toward treatment of the heart In cases of cardiac embarrassment, digitalis given intramuscularly (digifolin 6 c c) may be beneficial If there is profound cardiac collapse, strophanthin 1/120 grain (0 0005 gm) may be given intravenously, followed by intramuscular injection of digifolin, 3 to 5 c c. Other cardiac stimulants are used, particularly caffeine and epinephrine

Exophthalmic goiter sometimes occurs as a complication of diabetes, and may be responsible for precipitating diabetic acidosis It may be difficult to recognize hyperthyroidism in the presence of severe acidosis, Wilder and Boothby have advised considering administration of iodine in any case Sixty minims of compound solution of iodine in divided doses may be given by mouth or by rectum

Any patient who is in acidosis should have close attention, and if there is coma there should be constant supervision A stuporous or restless patient may become uncovered, or may fall out of bed unless he is watched The patient must be kept warm, using extra blankets and hot-water bottles if necessary Care must be taken, particularly for older people, to avoid burns of the feet from hot-water bottles or hot pads If patients have poor circulation, it is best to avoid entirely application of heat below the knees An enema should be given at the start and the bladder should be emptied by catheterization, repeated if necessary at regular intervals

The initial treatment should be followed by constant supervision until the patient is out of danger The emergency is not over until the patient has recovered consciousness completely, or until the carbon dioxide combining power is less than 30 One

can judge to some extent the patient's progress by clinical observation, but the values of laboratory tests cannot be overestimated Examination of the urine or blood sugar should be made before every injection of insulin Examination of urine only is of great value, but tests of blood sugar are even more important, unless the bladder is kept empty, the urine may still be found to contain sugar after the blood sugar has fallen Overtreatment with insulin must be guarded against, but enough must be given If the patient's condition is not critical, one may feel one's way and may depend on tests of urine without much difficulty If, however, the patient is critically ill the need for proper dosage of insulin immediately is so important that knowledge of the blood sugar is indispensable Determination of the carbon dioxide combining power is also important The patient who has a carbon dioxide combining power of less than 20 must have intensive treatment with insulin without delay If the value for carbon dioxide does not begin to rise within six hours, alkali may be needed

The after treatment of acidosis should not be neglected The patient may feel well within a day or two and he may think that he is ready to return to work, yet acidosis has such a profound effect on the whole body that a period of rest is essential Any patient who has had acidosis should be kept in bed for at least a few days A patient who has been in coma should be kept in bed at absolute rest for at least one week, and his return to activity should be gradual As soon as the appetite has returned, the full diet planned for maintenance may be given with the required amount of insulin The amount of insulin needed may change rapidly Large doses may be required at the beginning, but in a few days the amount may become much less If the urine remains free from sugar, the dosage should be gradually reduced until the condition has become stabilized

CAUSES OF FAILURE

Deaths from coma still occur because of failure to give adequate treatment when the condition has been recognized The great variability in response to treatment is responsible for

this unfortunate condition The danger from overtreatment must be kept in mind, as well as the danger from undertreatment The guidance which can be given by laboratory examinations is invaluable If possible a patient with severe acidosis or coma should be treated in a hospital with laboratory facilities It is just as important for a patient with acidosis to have care in hospital as for a patient with acute appendicitis Yet, patients are permitted to die without treatment in hospital, either because at the beginning it is thought that the condition is simple, or because finally it is thought the condition is too far advanced Yet, a patient who appears moribund may be brought back to life There is nothing more dramatic than the response to adequate treatment of patients with diabetic coma

PREVENTION

Emphasis must be placed on prevention of acidosis and coma This can be summarized in a few words If glycosuria is controlled, acidosis and coma will not occur Every diabetic patient should understand how to keep the urine free from sugar

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DIGESTIVE DISTURBANCES IN RELATIVES OF THE INSANE

WALTER C ALVAREZ

In 1928, the state hospitals of this country were taking care of 264,226 insane persons and 60,519 imbeciles and epileptics This makes a total of 324,645 persons with defective brains, or 1 in every 380 of the population In addition to these persons who are confined in asylums and easily listed by census takers, there are many more who are cared for in private hospitals or at home, others are overlooked because they are in an asylum for only a few years out of their life-time, and still others suffer from a mental unbalance so slight that its real nature is not recognized All that relatives and neighbors are likely to say about these persons is that they are queer, eccentric, ne'er-do-well, suspicious, dipsomaniac, "cracked on religion," or impossible to get along with Unfortunately, some of them talk so positively and so plausibly on many subjects that they get themselves elected to positions of great public trust. Taking all these men tally defective persons together, it seems to me that approxi mately one in 100 of the general population must be either insane, definitely psychopathic, epileptic, feeble minded, or nervously inadequate

But this is not all, because for every one of these persons there are a number of relatives abroad in the land, and surely some of them must have "picked something out of the family grab bag", not necessarily insanity, but often something that is almost as disabling and even more trying to the poor victim

I feel sure that a large part of the medical profession is as yet failing to recognize the nature of these troubles, and the worst of it is that the students now going through college are not being trained to grapple with this important problem which

is soon going to loom so large in their practices As a result, when they come to deal with these patients they will try to blame the troubles complained of on focal infection or organic disease of the digestive tract, they will put the patients to tremendous expense for useless laboratory examinations, and they will perform many useless operations Even when they recognize the fact that the brain is not working properly, they will be inclined to lay the blame anywhere but on a hereditary defect in this organ, they will insist on postulating some defect in the glands of internal secretion or in the functions of the colon

The cases now to be presented will serve to illustrate the type of complaints which I believe can be ascribed to the inheritance from insane or epileptic ancestors of a particularly unstable nervous system

Case I —An odd looking, taciturn type of man aged thirty-one years, a machinist, came to the clinic complaining of a "nervous stomach" which had bothered him for nine years As a youth he was energetic and tireless and he thinks he was normal in every way Then he received a slight blow in the upper part of the abdomen which didn't bother him at the time, and which, so far as he can see, could hardly have caused any trouble, but from that day onward the least exertion caused a peculiar type of air hunger

He consulted a physician who promptly removed the appendix in spite of the fact that there had never been any indigestion or abdominal pain On his return to work he found himself so short of breath that he had to stop and go home Again his physician operated on him, this time for the relief of a hernia Unfortunately the work was done under what was supposed to be local anesthesia and the patient suffered so much that he became completely unnerved The air hunger disappeared following this operation, but since that time the man has been ailing almost constantly He has been nervous, irritable and easily exhausted, and for the last two years has been unable to work He lost 30 pounds (13 kg) in weight because so often he was unable to eat

The curious feature about this man's indigestion is that if he eats alone he is likely to enjoy the food and to digest it well If, however, there are other people at table, and especially if there is any commotion, or argument, or annoyance from his children, he either finds himself unable to swallow, or else, if he does succeed in eating, the food remains for a long time in the stomach and is finally vomited Sometimes he can take only liquids for several days, and at other times he becomes so nervous and exhausted he has to go to bed The man now hates to be with people He is exceedingly irritable and tends to fly into rages He knows that he must never spank one of his children, because he might go into a blind rage and kill the child before he could stop One reason he cannot remain at work is because the slightest

effort on the part of his boss to hurry him gets him so flustered and irritable that he has to stop and go home to bed He is perfectly happy and well if he can take some food and drive out into the country for a day and he can work if no one is around to bother him

Physical examination showed a well muscled and fairly well nourished man who had something of the sullen appearance of many epileptics. The usual roentgen ray and laboratory studies did not reveal any abnormality As soon as I saw him and heard his story I felt certain that the cause of his trouble was to be found in a bad nervous heredity and questioning promptly brought out the fact that the mother was an epileptic, who for some time had to be confined in a sanatorium At times she was insane on religion A brother has had occasional attacks of epilepsy It certainly is unfortunate that such a man had to be operated on twice and had to spend considerable sums on useless examinations and Sippy cures before someone could recognize the fact that his gastro-intestinal symptoms are due to the extreme irritability of a congenitally defective nervous system

This man was intelligent enough to realize the nature of his predicament as soon as I discussed it with him, and he immediately made a good suggestion as to treatment. Having worked for years in the shops of the International Harvester Company, he is an expert in repairing farm machinery He plans therefore to fit up a little house and shop on wheels and to gypsy through the country picking up work here and there He is going to buy his wife a little store and for the good of all parties concerned he is going to live the solitary life that he craves and that he feels sure will bring back his health

Case II.—An unmarried woman aged thirty years complained of an aching pain and soreness in the region of the liver and attacks of what sounded like severe mucous colitis with nausea and vomiting At times there was so much disgust for food and so much vomiting that there was marked loss in weight There were spells in which she vomited steadily for several days The symptoms had been present off and on since girlhood The patient had never been strong and well and for years had found it difficult to earn a living because she had to spend several days out of every month in bed. Menstruation had always been very stormy with much pain and much psychic disturbance. Unfortunately a sterilizing dose of roentgen rays did not help much This woman had been through the hands of several prominent diagnosticians and innumerable examinations and diagnoses had been made. She had been cystoscoped and x rayed and psycho-analyzed and operated on until all her money was gone. Nothing significant had ever been found and nothing curative had ever been done.

As soon as I became conversant with this patient s problems I felt convinced that her main difficulty was not the aching distress in the region of

the liver, it was not the hypersensitive colon with the attendant constipation, and it was not the vomiting and insomnia, but it was her terrible and ever-present fear of poverty, of the county hospital and the state insane asylum She was an orphan without relatives who could help her, and hence she was dependent entirely on what she could make during the short intervals of time in which she was well enough to work Like so many psychopathic persons, she would get along fairly well for perhaps three weeks, during which time she would do excellent work, in fact, she would do too much, and would become worn out from long hours of effort During this time she would be fairly happy, and socially she could be decidedly entertaining and attractive Then suddenly, perhaps after a sleepless night spent in worrying either over mistakes of the past, or else over the precarious finances of the present, she would get up discouraged, sour on the world, disgusted with the follies of humankind, and even bitter and vindictive against the few friends who stayed by her and helped her in every crisis During the next ten days it would seem as if a devil had taken possession of her, sometimes in her tantrums she smashed the furniture, and in such spells it was only an unusually tactful nurse who could get along with her All her aches and pains became worse, she couldn't sleep, even with large doses of hypnotics, and she could not hold much food on her stomach Finally, when everyone was discouraged and wondering how she could ever get well, complete exhaustion seemed to bring sleep, and in a few days she would be back at work, again an able, and in many ways, a sensible and likeable woman As one would expect from all this, her nervous heredity was bad the mother died insane and the father, although brilliant and able, was eccentric and "a devil"

The only medicine that might have almost cured this patient would have had to take the form of a life annuity of, let us say, 1800 dollars This would have taken away the terrible fear of a bed in the city hospital which was always gnawing at her mind and keeping her from rest and sleep She had discovered that society has almost no provision for helping a refined and educated person who always manages somehow to look clean and neat and who cannot be happy in any but clean and respectable surroundings To make matters worse, when this woman was in one of her worst attacks she was too "difficult" to handle in a general hospital and not crazy enough for a state psychopathic hospital Actually then, the real problem was that of finding funds for her support, I had to induce a kind-hearted employer to give her work when she could take it, and to put up with her tantrums when she was in a fighting mood, and I had to find someone generous and kindly and tactful enough to care for her when she was in a semimaniacal spell One of the

hardest things to do was to convince her that even if she were to be cured of the vomiting and the abdominal pain she would still be facing, for her, the almost impossible problem of adjustment to life with her fellow men and women She could not seem to learn to live within her means of strength Like so many of these people, she worked too hard in her euphoric stage and as a result brought on the attack of depression and pain and insomnia

The feature of the case that I wish to emphasize here is that this type of patient is usually taken care of by gastro-enterologists, urologists, gynecologists, and surgeons, all of whom are inclined to act on the supposition that the source of the disease is in the abdomen And even when they fail to find anything wrong there, some of them continue to search in the same place I may be wrong but I believe that the real cause of the troubles of these patients is their bad nervous heredity, and the primary lesion, if one can ever be demonstrated, will be found, not in the abdomen, but in the brain and nervous system

Case III.—A married woman aged thirty three years complained of pain in the right side of the abdomen which she had had off and on for years. She said it was more a misery than a pain Some physicians diagnosed appendicitis but others who saw her in acute attacks with vomiting were satisfied that this was not the cause of the trouble She has always been sensitive to a number of foods. She is a belcher and is always constipated Even as a child she suffered with attacks of headache and vomiting and she has always had a tendency to be nauseated in the morning She has much burning and irritation of the bladder Like many nervous persons she feels weak and useless in the morning She cannot do much around the house on account of fatigue. She says she has never had any fun out of life. The one time when she does occasionally feel well is the week before menstruation As a girl she was supposed to have tuberculosis At times she has crying spells and definite hysterics. Shortly before I saw her she had had a breakdown with extreme nervousness bloating and distress after eating She felt dazed much of the time She had had much pelvic trouble and her two pregnancies were hard on her Nothing significant was ever found during the course of many physical and laboratory examinations.

To my mind the most important fact in this case is that the whole family is psychopathic and sickly The father was nervous and frail and couldn't stand having people around him The mother was confined in an asylum for a period of two years

It would seem obvious that the main trouble with this woman is now, and always will be, a psychopathic make-up, and any surgeon who ever operates on her must do so with the distinct understanding that he is not going to make her over into a well woman The most he can hope to do is to relieve some of the pain in the right side, and the chances are he will not succeed in doing this

Case IV —A man aged thirty-five years has been to the clinic several times complaining principally of a sense of weakness in his back, together with some vague indigestion He has always felt convinced that the weakness in the back is due to disease of the kidneys, and it is true that on one or two occasions he has seen blood in the urine As so often happens, a cause for this could not be found, but he seems to enjoy cystoscopic examinations, and from time to time he returns demanding another one For the last two years he has been unable to work, although he appears to be in perfect health and nothing abnormal can be found in the back

In talking with this man I noticed the peculiar look about the eyes which often suggests to me that I am dealing with a psychopathic person, and I soon drew from him the information that his sister has been in an asylum on account of melancholia He admitted that in many ways he was like this sister, and that he has her tendency to get spells in which he broods over the conviction that there is something seriously wrong with him

One of the most interesting features about the spells of depression complained of by these patients is that they often appear suddenly out of a clear sky The victim will be sure that from time to time something poisons him, and he will go from one physician to another insisting that the source of this toxin must be looked for and found He will say, "There must be something poisoning me because ordinarily I feel all right and then some morning I wake up and I feel 'awful' "

Case V —The feeling of poisoning just described was particularly marked in the case of a big man aged forty-two years who complained of spells in which he felt so weak and miserable that he just couldn't go to work Some days he was energetic, in fact, so much so that by working for an aggregate of perhaps two weeks in a month he was able to earn a good income Perhaps the most trying feature of his disease was that it was hard for his family and his employer to understand why a man who weighed 200 pounds, who looked the picture of health, and in whom many physicians failed to find anything organically wrong, should have to mope about the house three days out of every week

After studying this patient for some time I was impressed with his honesty and with the reality of his mental distress and his disability I was willing to accept his statement that some mornings he woke feeling so awful that he just couldn t talk business with anyone On asking him about his ancestry I found that his father was an eccentric person who may have been a little off' at times and who had streaks of mild melancholia similar to those of the patient Many of the consultants who have seen this patient have told him that his trouble is primary in the glands of internal secretion This may well be true but the difficulty is that they did not agree as to which gland is at fault he does not show any abnormalities of physical development and no one has as yet been able to help him by giving any form of glandular extract.

Although I believe that the trouble with most of these patients is in the brain, it is quite possible that disturbances in the glands of internal secretion, or abnormalities in metabolism, or smouldering infection somewhere in the body, or changes in the permeability of the bowel or liver with the resultant passage of toxic substances or bacteria into the blood stream, may play their part in bringing on the attacks If a toxin of some type is ever found in the blood of these patients I think it will be the same as that which brings on the attacks of melancholia in the other members of the family who are frankly insane

There is still another way in which the brain can be affected Studies made in *recent years on animals and men have shown* that certain bodily functions, and particularly the tendency to physical activity in females, wax and wane in a remarkably rhythmic way, and I believe that some of those ups and downs in health that are experienced by the insane and by their nervous and ailing relatives follow these rhythmic ebbs and flows in the chemical processes of the body At any rate, when I find a patient who suffers from sudden attacks of moodiness, depression and inability to face his fellows and his job, I do not feel as much need for postulating the presence of a toxin arising in the colon or in foci of infection as I might if I did not believe that the underlying mechanism is much the same as that which brings on cyclic attacks of insanity

Case VI.—A man aged thirty six years came to the clinic for advice in regard to a difficulty similar to that complained of in Case V There were days in every week when he was only 50 per cent alive. He would wake

in the morning feeling depressed and stupid and irritable and often his trouble would run on into a severe attack of migraine On such days he would not have been able to hold his job if it had not been that he was his own boss and could let up on his work This man had suffered much at the hands of several physicians who had removed his teeth and tonsils and appendix, and had made many diagnoses Nothing definitely wrong could ever be found with him, his physique was good, and no one would have guessed from looking at him that his health was bad

This patient's symptoms seemed to me to be so typical of what I have come to recognize as an "insanity equivalent" that I immediately asked him about his ancestry, and found that his brother was in an insane asylum with a severe form of epilepsy I gave him a small daily dose of luminal and to his delight he found that as this quieted his brain, the attacks of migraine and depression came at longer and longer intervals

Case VII.—A young woman aged thirty-two years complained of prostration and weakness, severe constipation, menstrual difficulties, and attacks of mucous colitis, all of which had confined her to a couch for most of her life At intervals surgeons had hopefully removed the appendix, an ovary, part of the colon, and the gallbladder The constipation was cured by the partial colectomy, but contrary to her expectations, proper evacuation of the bowel did not have much effect on the general condition

I was immediately impressed by the fact that the woman's prostration was out of all proportion to the amount of disease that could be found in her body I was impressed also by her confession that at times she was exhilarated almost to the point of mild mania and at other times she was depressed From girlhood she had been prostrated by the least excitement or the least attempt at work. In spite of all her illness she was a well-developed, fine looking woman, who was sensible, likeable, and usually pleasant and optimistic I had no sympathy with the physicians who at various times had read her the riot act, and I could not see how, through any mental effort, she could have greatly changed her situation or lifted herself out of her state of illness

A little study of this patient's heredity soon convinced me that her troubles were due primarily to a bad nervous ancestry An aunt is an eccentric recluse who has spent her life in bed, some members of the family are able, but others are eccentric and one has suffered from dipsomania

During the last twenty years I have been impressed by the number of these women with psychopathic ancestry who have diseased or abnormally functioning pelvic organs Many of them show signs of deficient function of the ovaries, and in many of them it seems to me highly probable that the defect in the brain is linked with defects in the glands of internal secretion, and particularly with defects in the structure and function of

the reproductive organs Another peculiarity is that the gradient of forces in the digestive tract is so flat or so easily reversed that the patients regurgitate or vomit with ease I have yet to see one of them whose regurgitation has been helped by any type of operation on the digestive tract

PATIENTS WHO ARE MILDLY INSANE

In addition to the group of patients whose troubles appear to be due to a nervous weakness or abnormality similar to that which has produced insanity of relatives, there is another fairly large group of patients who, although they insist that it is the gastro-enterologist who must help them, are really mildly insane I fear that in many cases the physician fails to recognize the real trouble with these patients largely because he is so annoyed by their unpleasant behavior Many of them from the start are somewhat sullen and suspicious or even definitely unfriendly Often it is impossible to thaw them out or to get a good history from them One of their most trying traits is their fondness for confronting the physician with two of his statements which are apparently contradictory and which they feel must represent an attempt at deception They are often abusive in speaking of every one of their previous medical attendants and, strange to say, the only persons for whom they have a kind word are the quacks whom they have met Even when the physician thinks that he has dismissed them in a satisfied frame of mind, he is likely soon after to receive a letter in which he is told in no uncertain terms that his diagnosis and treatment were wrong and worse than useless

It is particularly dangerous to operate on these patients because instead of improving they often get worse, they feel that they have been ruined, they become vituperative, and not infrequently one of them will start a lawsuit Altogether, they make most unsatisfactory patients

In my youth I used to spend hours and days trying to help these people, but as I grow older I hope to get enough sense to recognize them promptly for what they are, so as not to waste much time on them It seldom seems to do much good to talk

to them, they do not listen very well, they have their own favorite diagnosis, they are set in their own opinions and ways of doing things, and when they do express a desire to reform, they soon forget their resolves, or they find it impossible to change their habits of thought Unfortunately a sick brain cannot easily mend itself

Occasionally a patient suffering from insanity will talk so sensibly and will behave so properly that he or she is able to go through the hands of several physicians without arousing in the minds of any of them a suspicion of what the disease is This fact is well illustrated by the following case history

Case VIII —Three years ago a woman aged thirty-eight years began going to physicians for the relief of vague abdominal pains and indigestion which she felt sure must be responsible for the feelings of almost painful fatigue and depression that had come over her Unfortunately for her a few cysts of Endameba dysenteriæ were found in the stools They were thought to be the primary cause of her troubles and she was sent to a hospital for a strenuous course of treatment with bismuth emetin iodide, neosalvarsan, and other powerful drugs

She became much worse under this medication, but when a few more cysts were found, the treatment was repeated By this time the woman had become much depressed, she lost all interest in her home and her friends, she would not read, she would not leave her bed, and her only thought was about her bowels and the amebæ that were there

When I saw her I was immediately impressed by the fact that a fine-looking, well-nourished woman who did not show any sign of muscular weakness or atrophy could not be parted from her wheel chair, and the more I talked to her the more I became convinced that I was dealing with a case of mild melancholia with the usual loss of interest in the world round about I could not learn anything about the family heredity from her but a friend told me that for years her father had been insane On my advice the family ceased pestering the woman with examinations and treatments, not only they but the patient accepted the diagnosis of a mental depression, and faced the probability that improvement would be slow in coming A place was found in which she could get cheerful surroundings and good care, and I am happy to say that during the last year she has shown decided improvement, and is taking an interest in life again

COMMENT

It is a sad fact that as the training of physicians becomes more and more scientific they develop the bad habit of expecting to find in each patient something organically wrong that can

promptly be cured by medicine or surgery Too often the written history fails to record what to me is the most important fact, and this is that one or more of the patient's relatives are definitely psychopathic, epileptic, or insane I feel sure that many queer disturbances of digestion and other bodily functions are nothing more than manifestations of some hereditary disease or mutation which, in some members of the family, appears as a definite insanity Just as we physicians now speak of a migraine equivalent, so we may perhaps learn to speak of an insanity equivalent As I have shown, there are reasons for believing that the nervous abnormality which in one person produces a muddling of thought and a change in character may, in a relative, play miserable tricks with the involuntary nervous system that presides over the functions of the heart, the blood vessels, the digestive tract, and the glands of internal secretion

I have often been greatly helped in recognizing the serious mental condition of these patients by asking them if they can read Most of them say that when their spells are on them they cannot read because they feel too miserable, or because they have lost all interest in things about them, or because they cannot concentrate their attention or hold it on some subject for any length of time It is my conviction from studying these persons that whenever an intelligent man or woman who usually enjoys reading is unable to look at a magazine or book for more than a few minutes at a time the nervous system is in a dangerous condition of fatigue or disease, and no operative work of any kind should be undertaken unless it is absolutely necessary When patients are in this state, even the removal of teeth or tonsils, or any fatiguing or painful course of treatment is likely to bring on a nervous breakdown that may last for years

Often the best thing the physician can do for these patients is to make them see what their difficulty really is, and to teach them to adjust their lives so that they can live with the least amount of suffering and the greatest amount of efficiency The first thing they have to do is to give up their quest for a complete and permanent cure When they have only recently passed through a thorough diagnostic "mill" presided over by a well

trained diagnostician, and when nothing significant has been found, one of the kindest things the next physician consulted can do is to spare them the expense and discomfort of going through the whole process again Time can better be spent in an intelligent discussion of the problems of adjustment in home and office and the outside world

It would seem that the deans of medical colleges ought to make a greater effort to prepare the students for at least the recognition of insanity, and particularly for the recognition of the early stages of mental illness In most colleges the course in psychiatry is generally very short and the teacher who gives it will probably spend the time talking about the type of patient that he sees in hospitals Actually I think he would do the students immensely more good if he would talk about the patients that he does not see, because they go to the gastro-enterologist!

It doubtless would be well also if every medical student and physician could be compelled to read the odyssey of a certain Mrs Pierce who, when she showed typical symptoms of melancholia had to pass through the hands of many physicians before she could get the right diagnosis and intelligent treatment So far as one can judge from the story much of the treatment given even toward the end of her attack was unnecessary, but at any rate, after the passage of time she recovered, and, as so often happens in medical practice, the man who happened to be tinkering with her at the time got the credit for her cure

Unfortunately medical students are taught to take the family history first, actually it ought always to be taken last when the physician knows what he wants to dig for And usually he must dig, because some patients do not know anything about the family skeletons, others have forgotten, and many are secretive With most patients, it is impossible to get a history of insanity in the family until one has established friendly relations and has explained the value of the desired information in the matter of making a prognosis Even then, it is well never to ask about insanity but always about bad nervous breakdowns

POSTURAL HYPOTENSION REPORT OF A CASE AND REVIEW OF THE LITERATURE

NELSON W BARKER

Bradbury and Eggleston, in 1925, described the syndrome of postural hypotension and reported three cases Since then only twelve additional cases have been reported in the literature two by Ghrist and Brown in 1928, two by Ashworth in 1929, one by Riecker and Upjohn in 1930, one by Barker and Coleman in 1931, one by Sanders in 1931, and five by Laubry and Doumer in 1932 Laubry and Doumer called the syndrome "ortho static hypotension," which is possibly a better term However, judging from their rather limited report, only their first, second, and fourth cases can be accepted as cases of true primary postural hypotension as described by the other authors With a total of only thirteen reported and accepted cases in seven years, the condition must be considered rare, but it is probably more common than the literature would indicate, as its existence in a mild form or in its early stages may pass unrecognized unless the possibility of its occurrence is kept in mind The case following is reported as an example of the true syndrome of postural hypo tension, perhaps not quite as far advanced as in some of the other cases previously reported, the variations of the blood pressure were not immediately suggested by the patient's history

REPORT OF CASE

An unmarried American born farmer of Norwegian ancestry aged forty-one years, registered at the clinic July 15 1932, with the complaint of inability to perspire, which had resulted in great discomfort in hot weather His family history was negative, except that his mother aged sixty seven years had diabetes and recently had had a stroke. The patient had undergone appendectomy in 1905 and had had influenza in 1918 In March 1929 he had an attack of colic in the right upper portion of the abdomen and

jaundice, for which cholecystectomy had been performed The gallbladder was found to be subacutely diseased, and contained many stones Shortly after this, with the onset of warm weather, he noticed that he perspired very little over most of his body with the exception of the left side of the thorax which appeared to perspire normally When working in the sun he would become very warm and somewhat weak. Several times he had jumped into a river with his clothes on and had then gone back to work feeling much better The inability to perspire had not bothered him in cool weather, and the condition had not progressed in two years During the same period, and more particularly for the last few months, he had noted that sudden changes in posture had sometimes caused transient attacks of dizziness, characterized by weakness and dimness of vision, but never by loss of consciousness He had noticed these attacks particularly when suddenly standing up after having worked for some time bent forward Also, for the last two years he had had irregular, mild attacks of diarrhea Further questioning elicited the facts that he passed as much or more urine at night than in the day, particularly in cold weather, that his general health had been otherwise good, and that his complaints had not kept him from doing heavy farm work There had been no loss of libido or potentia

The patient was well-developed, appeared healthy and muscular, and looked his age Physical examination gave essentially negative results except that the skin was wet in the left axilla and over the left side of the thorax anteriorly, barely moist over the remainder of the left side, left arm and left hand, and was dry and hot over the head, neck, right side of the thorax, arm, hand, lower part of the back, abdomen, legs, and feet The day was warm (88° F), the patient's temperature by mouth was 99 6° F His blood pressure when recumbent was 130 systolic and 80 diastolic in millimeters of mercury, but when he stood it fell rapidly to 70 systolic and 55 diastolic where it remained while he was in this position The pulse rate rose simultaneously from 60 to 92 beats each minute, and there was a marked shrinkage in volume and softening of the radial pulse Urinalysis, estimation of hemoglobin content, and erythrocyte and leukocyte counts were normal, and a serologic test for syphilis was negative

Further observations were made on the patient's ability to sweat On another warm day (85° F) strips of cobalt paper applied to the skin revealed moisture in the areas before mentioned, and very slight moisture over the abdomen, back and legs, and none on the head, neck or feet When the patient was subjected to further heat from a heat chamber applied over the whole body, the sweating was only slightly increased in the wet and moist areas mentioned, and the patient became very uncomfortable He was given $\frac{1}{100}$ grain (0 006 gm) of pilocarpine hydrochloride by mouth without effect, but after $\frac{1}{6}$ grain (0 01 gm) of pilocarpine hydrochloride had been given hypodermically, profuse perspiration broke out over his entire body except his feet, which were just moist The sweating continued for more than an hour, during which time he said he felt very well, much better than usual on a warm day Similar, but slightly delayed sweating reactions were induced subsequently by the administration of $\frac{1}{5}$ grain (0 013 gm) of pilocarpine hydrochloride by mouth

Readings of the blood pressure were made by the mercury manometer and the pulse rates were taken in three positions on various days and at various times of the day during a period of six weeks The results are shown in Table 1 *It may be noted that the drop in pressure when passing from a*

TABLE 1

READINGS OF BLOOD PRESSURE AND PULSE RATE

Blood pressure millimeters of mercury						Pulse rate beats each minute		
Recumbent		Sitting		Standing		Recumbent	Sitting	Standing
Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.			
120	80	110	70	70	55	60	72	92
110	70	75	50	60	50	64	88	104
145	115	95	65	60	50	54	72	88
100	75	75	55	45	35*	68	92	108
150	100	105	80	80	65	54	72	88
145	95	110	75	70	50	60	84	104
150	100	115	80	60	40	56	72	84
135	85	90	70	62	48	60	72	88
140	100	100	70	60	40	64	88	108

* At time of this reading the patient had a mild attack of syncope.

TABLE 2

READINGS WITH THE PATIENT PASSIVE

Posture	Blood pressure.		Pulse rate beats each minute
	Systolic.	Diastolic.	
Horizontal	150	100	52
Head elevated 30	145	100	52
Head elevated 60	105	80	80
Vertical	80	65	84

recumbent to the erect position was never less than 50 systolic and 20 diastolic in millimeters of mercury and was as great as 90 systolic and 65 diastolic. It may also be noted that there was a definite increase of pulse rate coincident

with the fall in blood pressure The blood pressure stabilized itself for a certain posture in from one to two minutes after it was assumed There was an inconsistent slight difference in the blood pressure of the two arms, that of the right usually being 10 mm of mercury higher than that of the left, both systolic and diastolic in all three positions

Readings of blood pressure and pulse rate taken with the patient lying on a flat, adjustable table at different inclinations were as given in Table 2

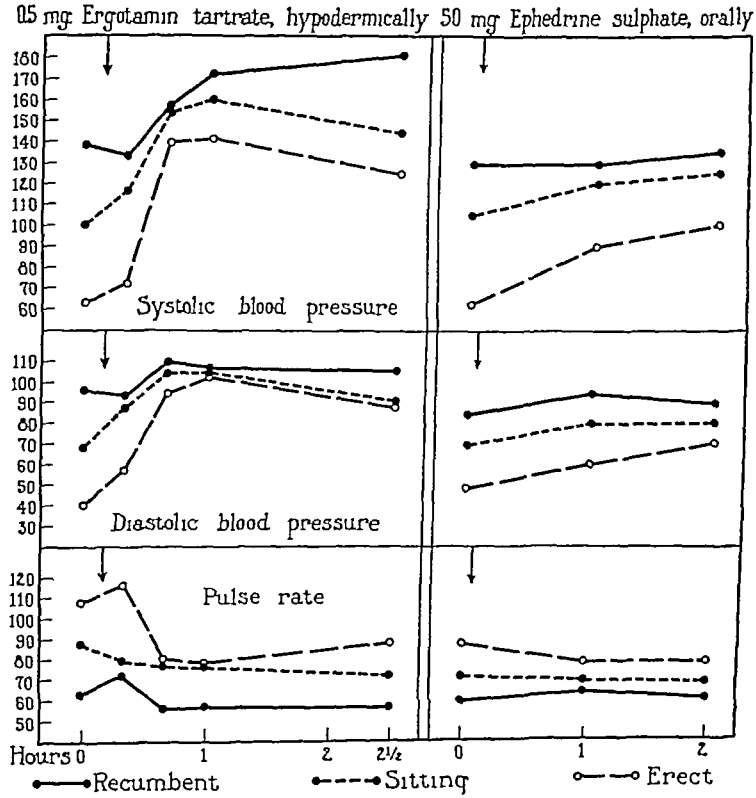

Fig 207 —The effect on the blood pressure and on the pulse rate of ergotamine tartrate and ephedrine sulphate with the patient in different postures

The effect on the blood pressure of 0 5 mg of ergotamine tartrate given hypodermically may be seen in Figure 207 There was a prompt and sustained rise in the blood pressure in all three positions, and a concomitant prompt and sustained fall in pulse rate There was also a tendency to lessening of the differences in blood pressures and pulse rates in the three positions However, the patient complained of muscular cramps while under the influence of this drug The same results, but to a less degree, were obtained after administration of 50 mg of ephedrine sulphate by mouth, cramps did not

develop (Fig 207) During the periods of objective influence of these drugs various quick changes in posture particularly the characteristic sudden straightening up after a period of bending forward failed to produce the slightest dizziness or syncope

Ergotamine tartrate given by mouth in doses of 0 5 mg 1 mg and 2 mg failed to produce any objective effect on the blood pressure. Ephedrine sulphate given in doses of 25 mg even as often as every two hours also failed to influence the blood pressure

The patient was advised to take $\frac{1}{5}$ grain (0 013 gm) of pilocarpine hydrochloride by mouth two or three times daily in hot weather particularly if he was going to work in the sun and to take 50 mg of ephedrine sulphate two or three times daily if he was going to do work requiring many changes in posture particularly from the bent over to the erect position Such a regimen has kept him comfortable, and has definitely reduced the number of mild attacks of syncope.

COMMENT

It was felt that the use of ergotamine tartrate was not practical in this case, but its definite objective effect suggests therapeutic possibilities for patients who have severe and frequent attacks of syncope, particularly if they cannot be controlled by the use of ephedrine

The case reported presents certain differences from those previously reported In spite of the consistent, striking drop in blood pressure when the patient changed from the recumbent to the erect posture, true syncope had never occurred and even mild syncope was noticed only occasionally and did not constitute a disability Possibly this is explained by the definite compensatory tachycardia, a phenomenon absent or incomplete in some of the cases previously reported Also, partial or complete anhidrosis with "increased distress in the summer months" had been noted in most of the cases, but in this case it was the chief complaint This leads to the suggestion that in any case of hypohidrosis or anhidrosis without the presence of organic disease of the sweat glands, postural hypotension should be excluded

Many otherwise normal persons notice mild and transient syncope after sudden change from a recumbent or sitting position to an erect posture This may be due to a slight lag in the mechanism responsible for maintaining cerebral circulation Ghrist has found in forty normal persons an average fall in

systolic blood pressure of only 1 mm of mercury and an average rise in diastolic pressure of 12 3 with passive change of posture from the horizontal to the vertical Coincident with this he found an average increase of 15 4 in the pulse rate each minute Although not all the cases of postural hypotension reported in the literature have manifested all the symptoms and signs described by Bradbury and Eggleston and in some the data are incomplete, they do agree in that there was a consistent and persistent drop of 50 mm of mercury or more in the systolic blood pressure when the posture was changed from recumbent to standing, a corresponding but smaller drop in the diastolic blood pressure, and in the symptoms of weakness and syncope, varying from occasional mild attacks to consistent severe attacks with complete loss of consciousness concomitant with this postural fall of blood pressure There is considerable difference in the increase of pulse rates with this change of posture in the different cases Data concerning the case reported to date are given in Table 3

Laubry and Doumer's third and fifth cases are not included in Table 3, because it is felt that they do not represent the same syndrome The third case was that of an elderly man who had a postural fall in systolic blood pressure of only 35 mm of mercury and this was associated with recurrent urticaria There were no mild attacks of syncope, and the condition disappeared when the urticarial attacks ceased The fifth case was that of a young woman who had a postural drop in blood pressure of only 40 mm of mercury, systolic, and this was associated with a mild state of exhaustion Both cleared after a period of rest Ashworth's second case is borderline, there were no attacks of syncope, but the postural hypotension was definite I have observed a case of secondary pellagra in which there was marked loss of tissue tonus due to malnutrition and a postural drop in systolic blood pressure of 20 mm of mercury with occasional mild syncope Striking postural hypotension has been noted in a few cases of Addison's disease This was observed by Ghrist in three of ten cases of Addison's disease, and in one case reported by Duggan and Barr Such cases may be classed as secondary

TABLE 3

DATA CONCERNING THE CASES REPORTED IN THE LITERATURE

Reporters	Bradbury and Eggleston			Ghrist and Brown		Ashworth.		Riecker and Uppohn.	Barker and Coleman.	Sanders.	Laubry and Doumer			Present report.
Case number in report cited Age years, and sex of patient	1 39 M	2 50, M	3 67 M	1 44 M	2 41 M	1 65 F	2 55 F	1 60, M	1 72 M	1 34 ML	1 48 M	2 47 M	4 62 M	1 41 M
Definite consistent postural hypotension, 50 mm. of mercury or more	+	+	+	+	+	+	+	+	+	++	+	+	+	+
Postural syncope severe, with loss of consciousness	++	++	++	++	++	+	0	0	+	+	0	0	0	0
Mild postural syncope or weakness	+	+	+	+	+	+	0	+	+	+	++	++	+	+
Variations in pulse rate with change in posture from recumbent to erect	60 66	60 62	65 80	80 88	80 84	60 70	66 80	72 84	60 100	60 70	?	68 76	?	68 108
Anhidrosis or hypohidrosis	++	++	++	+	++	+	+?	?	+	0	?	?	?	+
Increased distress in summer	?	+	?	?	+			?	0	0	?	?	?	+
Basal metabolic rate	−21	−13 −18	?	−7	−7	−16	−11	−1	−2	−17	?	?	?	?
Blood urea, mg per 100 c.c.	?	?	?	48	26	40	?	?	40	?	?	?	39	?
Greater urinary excretion at night	+	+	+	?	+	+	+	+	+	?	?	?	?	+
Loss of libido and potentia	+	?	?	+	+	−	−	?	?	0	?	?	?	0
False appearance of youth	+	+	0	0	+	0	0	?	0	0	?	?	?	0
Pallor	+	0	0	0	+	0	0	?	0	++	?	?	?	0
Secondary anemia	Slight	0	0	0	Slight	?	?	?	Slight	0	?	?	?	0
Organic changes in nervous system	0	0	+	0	0	0	0	0	?	0	0	?	?	0
Arteriosclerosis	0	0	?	0	0	?	0	+	++	0	?	?	?	0
Edema of legs	Slight	0	0	0	0	0	+	0	0	+	?	?	?	0
Diarrhea	0	0	0	0	0	0	0	+	0	++	?	?	?	+

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TABLE 3

DATA CONCERNING THE CASES REPORTED IN THE LITERATURE

Reporters	Bradbury and Eggleston.			Ghrist and Brown		Ashworth.		Riecker and Upjohn.	Barker and Coleman.	Sanders.	Laubry and Dounier			Present report.
Case number in report cited Age years, and sex of patient	1 39 M	2 50 M	3 67 M	1 44 M	2 41 M	1 65 F	2 55 F	1 60 M	1 72 M	1 34 M	1 48 M	2 47 M	4 62 M	1 41 M
Definite consistent postural hypotension, 50 mm. of mercury or more	+	+	+	+	+	+	+	+	+	++	+	+	+	+
Postural syncope severe, with loss of consciousness	++	++	++	++	++	+	0	0	+	+	0	0	0	0
Mild postural syncope or weakness	+	+	+	+	+	+	0	+	+	+	++	++	+	+
Variations in pulse rate with change in posture from recumbent to erect	60 66	60 62	65 80	80 88	80 84	60 70	66 80	72 84	60 100	60 70	?	68 76	?	68 108
Anhidrosis or hypohidrosis	++	++	++	+	++	+	+?	?	+	0	?	?	?	+
Increased distress in summer	?	+	?	?	+			?	0	0	?	?	?	+
Basal metabolic rate	−21	−13 −18	?	−7	−7	−16	−11	−1	−2	−17	?	?	?	?
Blood urea, mg per 100 c.c.	?	?	?	48	26	40	?	?	40	?	?	?	39	?
Greater urinary excretion at night	+	+	+	?	+	+	+	+	+	?	?	?	?	+
Loss of libido and potentia	+	?	?	+	+	−	−	?	?	0	?	?	?	0
False appearance of youth	+	+	0	0	+	0	0	?	0	0	?	?	?	0
Pallor	+	0	0	0	+	0	0	?	0	++	?	?	?	0
Secondary anemia	Slight	0	0	0	Slight	?	?	?	Slight	0	?	?	?	0
Organic changes in nervous system	0	0	+	0	0	0	0	0	?	0	0	?	?	0
Arteriosclerosis	0	0	?	0	0	?	0	+	++	0	?	?	?	0
Edema of legs	Slight	0	0	0	0	0	+	0	0	+	?	?	?	0
Diarrhea	0	0	0	0	0	0	0	+	0	++	?	?	?	+

postural hypotension, but in the thirteen cases in Table 3 no definite associated or primary disease was noted

Certain symptoms and signs mentioned in Table 3 can be regarded as the result of the postural hypotension, namely, the syncopal attacks, the slight increase in value for blood urea, the larger volume of urine excreted at night than in the daytime, the pallor of the face, and the edema of the legs The changes in the organic nervous system and the slight secondary anemia, occurring only occasionally, may be incidental Data revealed that the basal metabolic rate in half of the cases was subnormal This and the sexual dysfunction noted in three cases suggest that there may be associated disturbances of the endocrine system

One quite constant associated phenomenon, whenever observation has been made concerning it, is the partial or complete anhidrosis with increased distress in hot weather In three cases it was noted that this preceded the attacks of syncope It is also of note that the severe postural attacks of syncope with loss of consciousness did not occur in all cases, or they rarely occurred even when there was marked postural drop in blood pressure It is evident from the reports that in cases in which there were no severe attacks of syncope, a greater increase of pulse rate associated with the drop in blood pressure was present This indicates that there is an attempt to compensate for the postural drop in blood pressure by postural tachycardia in order to maintain the rate of blood flow through the organs, particularly the brain Less severe cerebral phenomena will occur if this compensation is at least partially accomplished

PATHOLOGIC PHYSIOLOGY

A review of the physiologic and pharmacologic studies in the reported cases of postural hypotension indicates that the physiologic abnormality consists in hypofunction of certain parts of the sympathetic nervous system This is manifested by loss of the reflex postural or orthostatic vasoconstriction necessary to maintain normal blood pressure against the force of gravity, by hypohidrosis or anhidrosis and, in advanced cases, by loss of reflex acceleration of the cardiac rate Failure of atropine to

increase the cardiac rate in advanced cases may be explained by the fact that although the effect of the vagus nerves is inhibited by this drug, the accelerator nerves are not functioning The accelerator effects of epinephrine and ephedrine are probably due to direct stimulation of the heart There is evidence that some vasoconstriction is produced by epinephrine and ephedrine in these cases This is slight following the use of epinephrine, more definite with the use of ephedrine Also, sweating can be produced in most of the ordinarily dry areas by administration of pilocarpine The site of action of all these drugs is said to be on the myoneural juncture Failure of the end-organs to react completely to drugs in cases of long standing disease may be due to disuse and atrophy of the end-organs or end plates, or both

Mild chronic diarrhea coming on with the other symptoms was reported by three patients whose cases are included in Table 3 Others reported increased constipation It is possible that these functional intestinal disturbances are also due to hypofunction of the sympathetic nervous system Hypofunction could occur anywhere in the sympathetic nervous system In none of the cases except Bradbury and Eggleston's third case was there any evidence of disease of the central nervous system The history in Ghrist and Brown's second case was of unilateral anhidrosis as the first symptom, and if this history is true, a disease originating in the central nervous system is suggested In other cases in which mention is made of it, the absence of sweating was patchy, at least at first. This, with the absence of other phenomena suggestive of a lesion of the central nervous system, raises the possibility of a peripheral or possibly of a ganglionic disturbance One might consider that the disturbance is due to partial hypofunction of the myoneural and neurosecretory end plates, and that only with vigorous stimulation of these, by ephedrine or pilocarpine, could the smooth muscle be made to contract and the sweat glands to secrete Against this hypothesis is the fact that in cases that are not too far advanced, pilocarpine in adequate doses the action of which is said to be on the end plates, produces definite and profuse sweating in areas that will not sweat reflexly under the

stimulus of heat This is a condition comparable to that which is observed after sympathetic ganglionectomy

Knowledge of physiology of the intergral parts of the central and peripheral sympathetic nervous system is still too meager to permit definite localization of lesions from peripheral effects All that can be said regarding the syndrome of postural hypotension from the data at hand is that the disturbance is probably in the sympathetic nervous system, is probably peripheral in most cases, and probably does not concern the myoneural structures primarily The persistence of symptoms and signs in most cases suggests that these disturbances have an organic basis The fact that Laubry and Doumer's third, fourth, and fifth patients recovered also suggests that, rarely, transient functional disturbances of the sympathetic nervous system associated with states of exhaustion may produce certain similar phenomena of postural blood pressure

ETIOLOGY

In those cases that may be considered organic, there is little to suggest the etiology In Sanders' case the symptoms came on abruptly following injury to the abdomen, and there was no hypohidrosis This suggests the effects of local trauma on the abdominal sympathetic nerves The incidence by sex is interesting Two patients only (14 per cent of the fourteen cases) were women, both were past the menopause and one of these had no symptoms Definite arteriosclerosis was present in two cases The possibility of gonadal insufficiency as a primary factor has been previously mentioned in view of the loss of libido and potentia These symptoms were not present in all cases, but in many the data are lacking, the symptoms may be secondary We would expect to observe the phenomenon of postural hypotension in other cases of definite testicular destruction if it were the primary cause Different causative factors might, of course, produce the same end-result on the sympathetic nervous system It is noteworthy that Ghrist and Brown's second patient died several years after their report was published, apparently of coronary disease

TREATMENT

The chief contribution to treatment was made by Ghrist and Brown, namely, the use of ephedrine sulphate The action of this drug is apparently twofold, producing tachycardia by direct cardiac stimulation, and a rise in blood pressure in all positions Both of these actions tend to prevent postural attacks of syncope It must be pointed out that doses of 25 mg may not be sufficient to secure an effect and that doses of 50 mg three to five times a day may be necessary Patients with advanced arteriosclerosis have not received much benefit from this drug, but it should be given a thorough trial There are certain objections to the use of ergotamine tartrate, but it is suggested that this be tried in doses of 0 5 mg hypodermically once or twice daily if ephedrine is not effective The definite relief of the hypohidrosis and of the distress secondary to it, reported here, by the simple use of pilocarpine hydrochloride by mouth in doses of ¼ grain (0 013 gm.) leads to the recommendation that it be used in other cases in which hypohidrosis is a distressing symptom

SUMMARY

A case of postural hypotension is reported in which hypohidrosis was the main complaint, and attacks of syncope were mild and infrequent The hypohidrosis and distressing symptoms secondary to it were relieved by the use of pilocarpine A review of the literature concerning the syndrome of postural hypotension indicates that the manifestations of the disease are due to hypofunction of the sympathetic nervous system, probably organic in origin There may be associated endocrine disturbances Cases of mild and transient postural hypotension have been reported and may be functional in origin Secondary postural hypotension may be associated with Addison's disease and states of malnutrition Ephedrine is the drug of choice when attempting to alleviate the phenomena due to postural hypotension

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PROGRESSIVE DISSEMINATED OBLITERATING ARTERITIS OF UNKNOWN ORIGIN

NELSON W BARKER AND GEORGE E BROWN

This case is reported because of the varied clinical manifestations, the difficulties in diagnosis, and the unusual type of vascular lesions

A married woman aged thirty nine years, American born of Polish parents registered at The Mayo Clinic, December 18 1930 with the complaint of a painful ulcer of the left forefinger Her family history was negative except that her mother had died of cardiac disease at the age of fifty six years The patient had been married seventeen years and had had one child who died in infancy Her past history was negative except for influenza in 1918 and mild menorrhagia in 1929 which was relieved by dilatation and curettage. The patient had never used tobacco There was no history of phlebitis She stated that for seven years on exposure to cold she had had blanching of all the fingers of both hands except the thumbs This had been noted particularly in cold weather and had been getting worse each winter At first only the distal phalanges were involved but for the last year the entire fingers had become white. Rubor followed the blanching Cyanosis had not been noted Involvement of the toes or feet had not been noted One month before admission a dark painful area appeared on the tip of the left forefinger near the nail This was incised and a drop of pus evacuated a small ulcer formed which did not heal

Physical examination revealed that the patient was well-developed and well nourished The ocular fundi were apparently normal There was a small adenoma of the left lobe of the thyroid gland Percussion revealed slight increase in the transverse diameter of the area of cardiac dulness and there was an apical systolic murmur which was not transmitted Pulsations were of normal volume in both femoral popliteal anterior and posterior tibial brachial radial and ulnar arteries although at times the left ulnar artery seemed to have a weaker pulsation than the right. There was a dry crusted ulcer 3 mm in diameter on the tip of the left forefinger and the distal phalanx of this finger was slightly cyanotic. Neurologic examination gave negative results. The blood pressure in millimeters of mercury was 130 systolic and 80 diastolic. Urinalysis was negative The concentration of hemoglobin was 17 2 gm in each 100 c.c. of blood erythrocytes numbered 4 590 000 and leukocytes 8 400 in each cubic millimeter of blood The Wassermann reaction of the blood was negative. A roentgenogram of the left hand was negative.

A diagnosis was made of Raynaud's disease, with a trophic ulcer of the left forefinger

December 24, 1930, bilateral cervicothoracic sympathetic ganglionectomy and trunk resection was performed by Craig The patient's convalescence was uneventful The fingers remained pink, warm, and dry The ulcer healed in two weeks

The patient returned for reëxamination four months later There had been no more changes in color or trophic changes of the fingers The hands were warm and did not sweat There was a slight, residual Horner's syndrome Otherwise, the results of the examination were the same as of the previous examination, and the patient had no complaints

July 16, 1931, the patient was brought to the hospital in an ambulance. She had remained well until May 15, when a red, blotchy rash had appeared on her legs This lasted a few days and then disappeared, but recurred several times when she was active on her feet Her physician at home described the rash as having a purpuric appearance July 8 she had a chill in the evening, July 9 she had a second chill, with backache and aching in the legs Following the first chill her temperature rose to 101 6° F July 11 she first noticed numbness of both hands to the wrists Her feet felt dead and heavy, and there was some aching in both the hands and the feet July 15 her temperature rose to 105 6° F and she had a slightly bloody discharge from the nose

Examination July 16 revealed a red, dry tongue, and slightly reddened pharynx The ocular fundi were negative By percussion there was an increase in the area of cardiac dulness, the transverse diameter being 14 cm There was a soft systolic murmur, best heard at the pulmonic area, transmitted to the apex. Nothing abnormal was found in the lungs, abdomen, pelvis, or rectum There was definite left wrist drop and weakness of the extensor muscles of the right wrist There was also weakness of flexion and extension of the fingers of both hands There was weakness of dorsiflexion of both feet The biceps and triceps reflexes were markedly diminished Supinator, patellar, hamstring and Achilles reflexes were absent Babinski's and Hoffman's signs were absent There was some diminution of vibratory sensation in both ankles There was tenderness along the course of the median, ulnar, radial, sciatic, and peroneal nerves There were a few fading red maculæ around the ankles, which appeared to be purpuric. Her temperature on admission was 102° F , the pulse rate was 110 beats each minute The blood pressure was 110 systolic and 70 diastolic in millimeters of mercury Urinalysis disclosed a trace of albumin and a few pus cells The flocculation test for syphilis was negative The concentration of hemoglobin (Dare) was 68 per cent, erythrocytes numbered 4,410,000 and leukocytes 20,650 in each cubic millimeter of blood The percentages of the various types of leukocytes were as follows neutrophils 56, eosinophils 0 5, monocytes 15, and lymphocytes 28 5 A roentgenogram of the lungs was negative The pressure of the spinal fluid was 12 5 cm of water, with prompt response to pressure on the jugular veins, Wassermann and Nonne tests on the spinal fluid were negative, there was one small lymphocyte in each cubic millimeter, and the value for total protein was 70 mg in each 100 c c Culture of the blood gave negative

results. Agglutination tests for Alcaligenes abortus Eberthella typhi (Bacillus typhosus) Salmonella paratyphi (Bacillus paratyphosus A) and Salmonella schottmülleri (Bacillus paratyphosus B) were negative Cultures of the nose and throat were negative for Corynebacterium diphtheriæ.

The opinion of the consulting neurologist Moersch was that there was definite peripheral neuritis or neuronitis With the fever leukocytosis and high protein content of the cerebrospinal fluid acute anterior poliomyelitis was considered a possibility Two more cultures of the blood gave negative results Intradermal wheal tests with poliomyelitis streptococcus antigen (Rosenow) gave negative results Poliomyelitis antistreptococcus serum was given daily for twelve days without change in neurologic findings. The possibility of poisoning with a heavy metal was also considered The urine was negative for arsenic, but the first specimen contained 0 2 mg of lead in 1 liter Sodium thiosulphate (0 5 gm) was given intravenously for four days analysis of the urine for lead was negative on each day of this period Two weeks later further analyses of the urine for lead were made on four different days One specimen contained 0 03 mg in each liter and one 0 05 mg in each liter the other two specimens were negative for lead

The patient s temperature varied between 101 and 104 F It continued to be elevated daily but rose a little less each day for four weeks. On the twenty ninth day it remained normal for the first time. The leukocyte count slowly decreased On the twenty ninth day it was normal and the differential count was normal From the twenty ninth to the fifty sixth days the temperature varied daily between 98 and 99 F in the morning and from 99 2 to 100 F in the evening There was very slight improvement in the paralysis. The urine was persistently normal

On the fifty-seventh and fifty-eighth days the patient had attacks of severe colicky pain in the left upper quadrant of the abdomen associated with diarrhea With these attacks the temperature in the afternoon rose to 101 F Similar attacks occurred on the sixty third and sixty fourth days and again on the sixty ninth seventieth and seventy first days. At this time the stools contained blood in small amounts but no pus or parasites. Another culture of the blood was negative at this time. On the seventy fourth day it was noted that the patient was becoming apathetic, morose, and depressed. This represented a definite change in personality On the seventy fifth day weakness of the right inferior rectus muscle developed with diplopia which lasted for several hours

On the seventy seventh day the tip of the right second toe became blue and painful. The pain gradually subsided but a dark purple area remained with a definite line of demarcation On the seventy eighth day a few scattered purpuric lesions appeared over the lower parts of both legs. Albuminuria, graded 2 was noted at this time and continued The concentration of urea was 18 mg in each 100 c.c. of blood At this time examination of the blood revealed a concentration of hemoglobin of 59 per cent erythrocytes numbered 4 110 000 and leukocytes 14 500 the coagulation time was seven and a half minutes, and bleeding time two minutes The platelets numbered 56 000 in each cubic millimeter of blood Clot retraction was complete in one hour and fifteen minutes. At examination the heart was unchanged

except that the transverse diameter was now 16 cm by percussion The blood pressure was 130 systolic, and 74 diastolic The blood pressure was 146 systolic, and 92 diastolic on the eighty-seventh day, 142 systolic and 94 diastolic on the ninety-fourth day, 156 systolic and 98 diastolic on the hundred and eighth day The temperature continued to range from 98° to 100° F From the hundred and ninth to the hundred and fifteenth days there was another episode of abdominal cramps and diarrhea, with blood and pus in the stools and afternoon fever of 101° F On the hundred and fourteenth day

Fig 208 —Patient's arm during terminal stages of illness, purpuric lesions with ischemic ulcer and also gangrene of the third and fifth fingers may be noted

a purpuric spot, 2 cm in diameter, appeared on the dorsum of the right foot A bleb appeared in the center of this and then dried, leaving a purple black area which persisted On the hundred and eighteenth day, similar but smaller lesions appeared on the third right finger and on the dorsum of the left foot, and on the left heel Platelets numbered 65,000 and 74,000 on two occasions

Following this there was a period of improvement which lasted for two weeks The mental depression and apathy disappeared There was some

improvement in the muscular weakness, particularly of the hands The temperature fell slowly to normal

On the hundred and thirty fourth day the temperature rose to 101 6 F the patient complained of cough and dyspnea The lungs were negative except for a few râles at both bases On the hundred and thirty fifth day the cough and dyspnea had increased Examination disclosed signs of some fluid in the left side of the thorax. The patient had attacks of dyspnea and cyanosis and leukocytes numbered 16 400 in each cubic millimeter of blood A bright red rash appeared on both arms consisting of discrete macules 1 to 10 mm in diameter On the hundred and thirty-seventh day there was definite evidence of consolidation at the base of the right lung The fever continued the temperature ranging from 101 to 104° F The blood pressure was 170 systolic and 100 diastolic. A punched-out ulcer 0 7 cm. in diameter appeared on the left side of the soft palate.

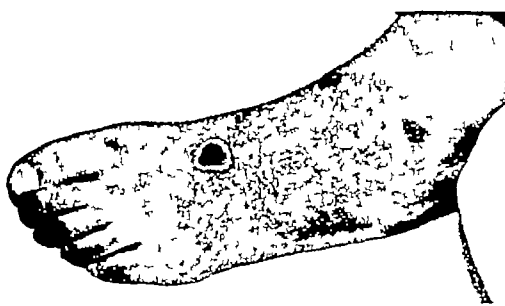

Fig 209 —Patient s foot during terminal stages of the disease an ischemic ulcer on the dorsum pigmentation and dryness of the skin are present.

On the hundred fortieth day edema of the arms, legs and back was noted. The patient was very drowsy There was acute retinitis with mild edema of the disks numerous cotton wool patches and some hemorrhages. The arteries were narrowed with some irregularity and there was scattered venous thrombosis. The rash on the arms had become darker and looked more purpuric numerous purpuric patches appeared on the thighs and back. On the hundred and forty third day the terminal phalanx of the third and fifth fingers of the right hand became gangrenous (Fig 208) On the hundred and forty fourth day the tips of the left second and third toes and of the left fourth finger became gangrenous (Fig 209) The temperature remained high 101 to 105 F and the patient became more drowsy each day The left second and third fingers became gangrenous the edema increased and the patient became comatose and died on the hundred and fifty third day

Summing up the clinical findings in this case we have a typical syndrome of Raynaud s disease of the fingers which apparently had been completely

relieved by cervicothoracic sympathectomy Six months later a fatal illness of five months' duration developed, which had the following characteristics (1) Chills and fever at the onset, and an irregular febrile course during the entire period, (2) neuronitis of all four extremities at the onset, with relatively little subsequent improvement, (3) some evidence of cerebral involvement for a period during the course of the disease, (4) scattered cutaneous and digital occlusive vascular lesions, purpuric spots and cutaneous infarctions, becoming more numerous in the terminal stages, (5) episodes of diar-

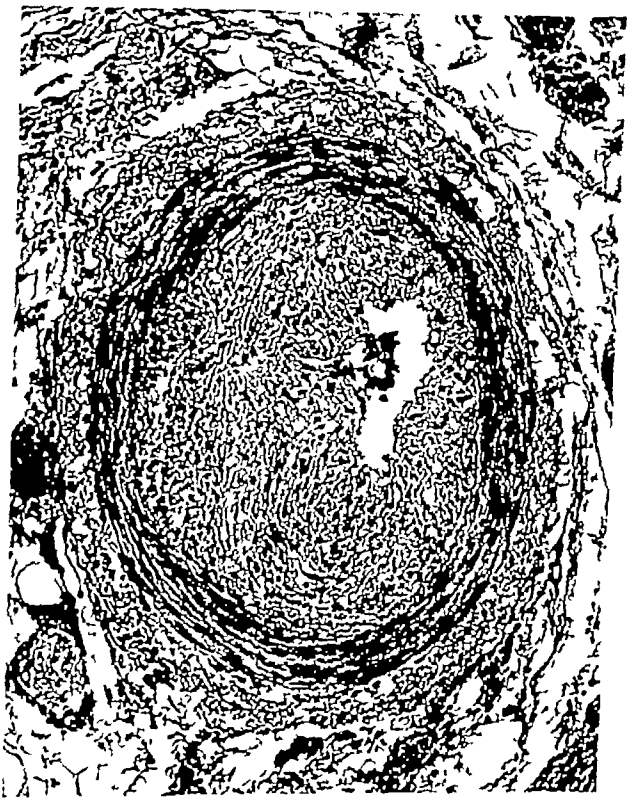

Fig 210—Small artery in the serosa of the colon (× 95) There are marked proliferation and some degeneration of the endothelium of the intima, and thinning of the media

rhea and abdominal cramps, with blood and pus in the stools, (6) persistent mild albuminuria without abnormal retention of urea in the blood, irregular leukocytosis, low blood platelet count, persistently negative blood cultures, absence of definite signs of a cardiac lesion other than enlargement, and (7) terminal consolidation of the bases of the lungs, hydrothorax, anasarca, rising blood pressure, and retinitis

Necropsy was limited to the thorax and abdominal cavities An abstract of the gross findings is as follows

There was about 50 c.c of blood tinged fluid in the left pleural cavity and 100 c.c. in the right pleural cavity The pericardial cavity contained 500 c.c. of clear straw-colored fluid The heart weighed 410 gm A conical depression 1 cm in diameter and 1 5 cm deep was found in the left side of the interventricular septum near the apex with a gray scar in the corresponding area on the right side. Otherwise the myocardium was without gross changes The pericardium and heart valves appeared normal There was slight sclerosis of the coronary arteries without evidence of occlusion

Fig 211.—Small artery and arteriole in the lumbar nerve plexus (× 40) Lymphocytes fibroblasts and endothelial proliferation may be noted

In the posterior portion of the lower lobe of the left lung there was a dark red consolidated region 5 by 4 by 3 cm. in diameter the artery and vein supplying this region were occluded by red thrombi. The lower lobe of the right lung was firm and dark red with nodular areas throughout of even firmer consistence These nodules had necrotic centers one of the arteries to this lobe was occluded by a red thrombus. The spleen weighed 415 gm but otherwise appeared normal The liver weighed 1 917 gm and appeared normal externally and on cut section except for a few small circumscribed

areas which were light yellowish brown The gallbladder contained three necrotic ulcers, 2 to 4 mm in diameter There were small ulcers 1 to 2 mm in diameter in the terminal portion of the ileum, and irregular ulcers with hemorrhagic bases in the colon at the hepatic and splenic flexures The right and left kidneys weighed 155 and 140 gm , respectively Their surfaces were deep purplish red, with multiple, regular, depressed scars which were much paler The cut surface showed that the cortex alternately was deep red and grayish brown, corresponding with the surface

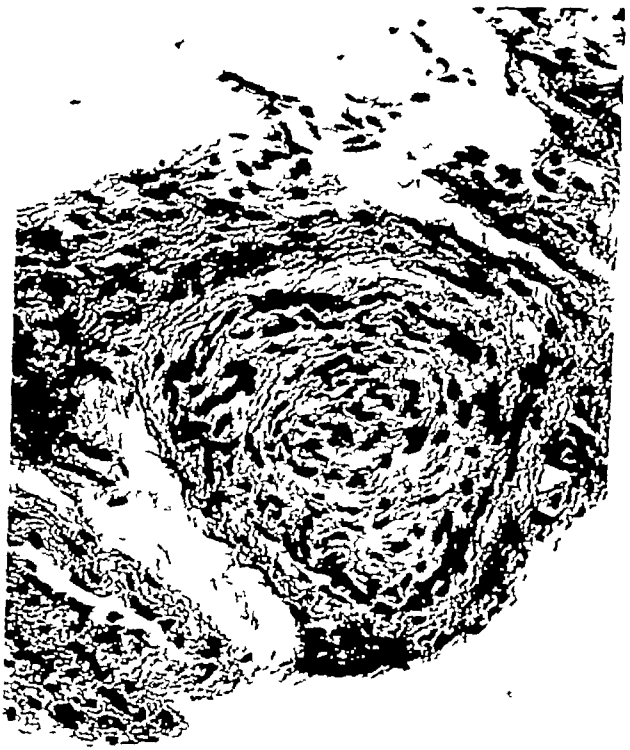

Fig 212 —Arteriole of the pectoralis major muscle (× 220) Lymphocytes, fibroblasts in the media, and endothelial proliferation with complete obstruction of the lumen are present

The suprarenal glands, urinary bladder, uterus, fallopian tubes, ovaries, thyroid gland, pancreas, and esophagus appeared grossly normal There were red thrombi in both internal iliac veins There were a few yellowish plaques in the aorta, which otherwise appeared normal The spinal cord was slightly swollen and had numerous localized areas of softening The lumbosacral and brachial nerve plexuses, and the lumbar sympathetic ganglia, appeared normal grossly

Histologic examination showed that in the septal defect of the heart the muscle fibers were small and separated by fibrous tissue and there were several areas of solid fibrous tissue The lesions in the lungs were mainly hemorrhagic infarcts but in the lower lobe of the right lung numerous small patches of bronchopneumonia were found with exudates of polymorpho nuclear leukocytes in the alveoli and bronchioles The thrombi in the arteries and veins of the lung appeared to be of recent origin showing only early signs of organization

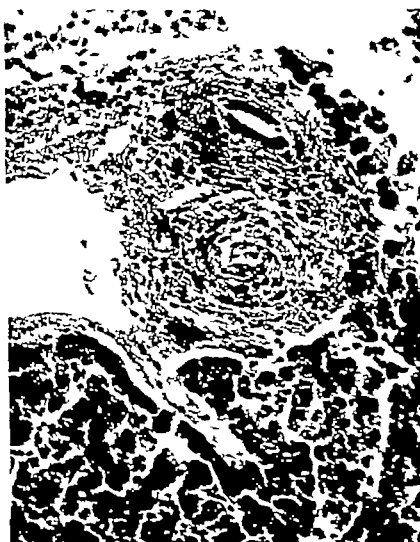

Fig 213.—Arteriole of the liver (× 200) There are reduction in the size of the lumen and thickening of the media with scattered lymphocytes.

Arterial lesions of a definite type were found in the liver serosa of the stomach and colon pectoralis major muscle, subcutaneous tissue beneath the cutaneous infarctions kidneys pancreas broad ligaments, leptomeninges of the spinal cord and in the lumbar and brachial nerve plexuses (Figs. 210–213) About 25 per cent of the small arteries seen in these organs were affected The lesions were of two types. In arteries 200 to 1 000 microns in diameter there was proliferation of the endothelial cells which appeared large and polygonal and encroached on or even totally obliterated the lumen The

muscle walls of some of these were thinned as if by pressure from within In the kidneys there were various degrees of degeneration of endothelial cells of the arteries, and the cells were replaced in some regions by an irregular hyaline mass partly occluding the lumen and containing few cell nuclei A large number of the arterioles 50 to 200 microns in diameter in the various organs mentioned had thickened media, with increase in the number of medial nuclei, intimal proliferation, definite lymphocytic collections in the adventitia, and in some instances lymphocytes in the media also In the liver, one of the branches of the portal vein was found to be occluded by a fresh thrombus, and there were many lymphocytes in the adventitia The yellow zones in the liver consisted of atrophic cells, with widened sinuses and some deposits of fat There was a moderate amount of central necrosis and congestion through out the liver The spleen was markedly congested The ulcers in the colon and gallbladder extended into the muscularis, and there was relatively little cellular reaction in their margins Occluded arteries were found in the serosa beneath these ulcers The scars in the kidneys were of the type associated with slowly developing ischemia, regularly spaced, with atrophic or absent tubules which were replaced by fibrous tissue, glomeruli in these scars appeared normal The normal regions in the kidneys appeared con gested In the spinal cord were small patches of vacuolation beneath the pia at all levels, chromatolysis of ganglion cells, and irregular loss of myelin The ganglion cells of the anterior horns were changed but little

In the lumbar and brachial plexuses some nerve bundles appeared normal, but in others there was extensive loss of myelin

Culture of the blood was negative. Cultures from the lungs and kidneys yielded green-producing streptococci

Analysis for lead was made of some of the tissues (Table 1)

TABLE 1

ANALYSIS OF SOME OF THE TISSUES FOR LEAD

	Tissue, gm	*Lead, mg*
Aorta	46 0	0 07
Spinal cord	2 4	0 10
Kidney	28 3	0 14
Liver	21 1	0 00

The anatomic diagnosis was (1) Diffuse nonspecific arteritis of small arteries and arterioles, (2) recent thrombosis of internal iliac veins, (3) diffuse miliary subpial myelomalacia (ischemic), (4) localized ischemic degeneration of peripheral nerve trunks, (5) chronic ischemic atrophy of the kidneys, (6) ulcerative ileitis, colitis, cholecystitis (ischemic), (7) partial gangrene of fingers and toes, gangrenous ulcers of the feet, hands, and left side of the thorax (8) infarctions of the lower lobes of both lungs with bronchopneumonia, early pleuritis and bilateral hydrothorax, (9) splenomegaly, (10) chronic passive congestion of the liver with central necrosis and localized thrombosis of the hepatic veins, (11) hydropericardium, and (12) scar of interventricular septum of heart

COMMENT

The findings at necropsy supported the clinical data that the primary lesion was a scattered but widespread occlusive arterial disease with various visceral and cutaneous manifestations due to slow and rapid infarction The large arterial trunks were spared In the small arteries only the intima was affected In the arterioles there were evidences of inflammation of all three coats It is impossible to say whether the primary lesion was in the small arteries or arterioles The histologic picture is different from the rather violent inflammatory reaction of thrombo-angiitis obliterans, and lacks the medial degeneration of arteriosclerosis Somewhat similar but less striking changes in arterioles have been observed by us occasionally in specimens removed for biopsy of the pectoralis major muscle in cases of severe or malignant hypertension

Some of the clinical phenomena are suggestive of those which have been observed in cases of periarteritis nodosa However, the pathologic picture lacks the definite nodules, adventitial reaction, and the medial necrosis and degeneration ordinarily found and described in cases of periarteritis nodosa The simple endothelial proliferation in this case, occurring in the small arteries, which can be called a true obliterating endarteritis, is described by Kaufmann as a nonspecific change observed after disuse, simple thrombosis, ligature, surrounding inflammation, and various infectious and toxic injuries

Three somewhat similar cases have been found in the literature The case reported by Perla and Seligman occurred in a woman, aged forty seven years The arterial lesions described were much the same The heart and brain were the organs mainly affected, but ischemic lesions were found in the lungs, spleen, kidneys, and extremities Gangrene of the toes occurred in the terminal stages, and there was thrombosis of the vena cava. The Wassermann reaction of the blood was 4+, that of the spinal fluid was negative

The case reported by Trabaud and Chaty was that of a Mohammedan girl, aged twenty years Asymmetric mass gangrene of three fingers of each hand and of four toes of the right

foot developed, and then, within thirty-eight days, cyanosis of the legs and arms, gangrene of the tip of the nose, right ear and skin over the sacrum, heels, trochanters and elbows occurred There was no evidence of syphilis, as serologic tests of the blood and spinal fluid were negative There were no neurologic lesions At necropsy the larger arterial trunks were not affected, but there was marked proliferation of the intima, leading to obliteration of the small arteries and arterioles of the extremities, kidneys, and ovaries The authors considered this case as Buerger's disease (thrombo-angiitis obliterans) The sex, age, rapid progression, widespread lesions, and absence of involvement of the larger arteries make such a diagnosis hardly justifiable

Branson reported a patient, aged twelve years, whose chief lesion he stated was widespread endarteritis of the kidneys and brain The medial coats of the arteries were not involved Baehr has found rather widespread vascular lesions in cases of nonrheumatic verrucous endocarditis, consisting of swelling, proliferation, and necrosis of the endothelium, with greater or lesser degrees of obliteration of the lumina occurring in capillaries, arterioles, small arteries and small veins Although this is a different appearing lesion, it may be related in its manner of production

As to the etiologic agent responsible for the arterial changes in our case, we can only speculate Lead poisoning must be considered The clinical neurologic manifestations and the abdominal cramps were suggestive Lead was being excreted in the urine at times during life Fairly large amounts of lead were found in the aorta, spinal cord, and kidneys after death Against lead poisoning was the absence of anemia and lead line There is little in the literature concerning the exact nature of the vascular lesions caused by chronic lead poisoning Most pathologists give lead poisoning as a cause of arteriosclerosis of the degenerative type Aub and his associates expressed doubt of the specificity of any arterial or renal lesion for lead poisoning, and questioned whether the arterial lesions described in cases of lead poisoning have been due to lead In Timme's case the lesion was essentially in the media of the larger arteries Kazda's

cases suggested thrombo angiitis obliterans Ophüls was not able to produce arterial lesions in animals with experimental lead poisoning Data concerning the amount of lead in the body or in different organs necessary to produce vascular or other visceral lesions are lacking It is possible that the finding of lead in the urine and tissues in our case was accidental, and that the lead was not a factor in the disease

The chill and leukocytosis at the onset, and the long continued fever, are very suggestive of chronic infection However, no foci of infection were found during life or at necropsy Cultures of the blood were repeatedly negative during life Green-producing streptococci found in the lungs and kidneys at necropsy may well have been terminal invaders The lesions seem to suggest a reaction to a toxin of bacterial rather than of chemical origin

Other interesting features of the disease were the preceding Raynaud's syndrome, the relationship of which to the organic vascular disease is doubtful, the low platelet counts, and the progressive rise in blood pressure, apparently secondary to true organic vascular disease

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PARANEPHRITIC ABSCESS REPORT OF TWO CASES

JOHN M BERKMAN

Habein, in 1929, in a consideration of the etiology of peri nephritic abscess, stated that cortical abscess of the kidney is the most common cause of the condition He also emphasized the metastatic relationship of this type of renal infection to superficial infection, such as boils, carbuncles, or abscesses The next cause of perinephritic abscess, in order of frequency, is extension of other infectious processes beginning in the urinary tract, and complicated by pyonephrosis, renal calculus, and so forth, leading to renal involvement Although rupture of the bowel, especially the appendix, is usually included in consideration of the etiology of abscess about the kidney, it is a very unusual cause when compared to the others mentioned, furthermore, the resulting condition probably should be called "para nephritic" abscess, as Dr Cabot will explain Because, in the last two years, two cases of carcinoma of the splenic flexure of the colon which were responsible for pararenal infection have been seen at the clinic, it seems justifiable to call attention to them

In the two cases reported here the presence of a paranephritic abscess was clearly apparent clinically, but because of absence of a suggestive history, and lack of evidence, its relation to a lesion of the colon was not suspected

REPORT OF CASES

Case I.—A man aged forty seven years, came to the clinic May 13 1930 complaining of pain in the region of the left kidney associated with fever which had been present continuously for a period of six weeks. Two years previously he had had what apparently was right renal colic this subsided, and he had experienced excellent health until the onset of fever and pain The onset of fever occurred abruptly and at first was associated with discomfort in the left lower part of the abdomen which lasted only a few days.

Following this, pain and tenderness appeared in the region of the left kidney There were no urinary symptoms Since the onset of his illness his appetite had been poor, and there had been some loss of weight Gastro intestinal symptoms were lacking, except for slight constipation, which had been present since the onset

The patient looked very ill With the exception of extreme tenderness over the left renal region, examination was negative The temperature was found to vary between 100° and 104° F The urine contained albumin, graded 2, and pus, graded 1 Leukocytes numbered 11,000 in each cubic millimeter of blood The flocculation test for syphilis, agglutination test for undulant fever, Widal test, and agglutination test for paratyphoid fever A and B were negative The value for urea was 28 mg in each 100 c c of blood, and the phenolsulphonphthalein test 15 per cent Roentgenograms of the thorax showed an elevation of the left side of the diaphragm, and roentgenoscopic studies of the kidneys, ureters, and bladder were negative

May 16, exploration was made for left paranephritic abscess, and about 180 c c of thick, greenish, odorless pus was drained Following the evacuation of pus, the cavity was explored, and two cavities about 3 cm in diameter were found, which seemed to extend into the renal substance The temperature remained between 100° and 104° F for about two weeks, then gradually returned to normal The patient was dismissed on the twenty-fifth postoperative day

September 24, 1930, eighteen weeks after operation, the patient was readmitted to the hospital because of pain in the left renal region, which at times was referred to the left lower abdominal quadrant He was not feverish, but had not improved as much as he should have At that time leukocytes numbered 8,600 in each cubic millimeter of blood, and the value for hemoglobin was 55 per cent September 27 exploration was made again, and the left kidney was found to be normal in size and consistence, anterior to it was a mass approximately 10 cm in length and width A specimen for biopsy was taken from the mass the pathologic diagnosis was adenocarcinoma, graded 4 The diagnosis was carcinoma of the colon with extension to adjacent structures

Case II —A woman, aged fifty six years, was admitted to the hospital on June 1, 1932, giving a history of weakness, pallor, and shortness of breath She apparently had been well until January 22, 1932, on which day she had remained in bed on account of dizziness The following day she went back to her work, and continued working intermittently until March 3 However, during that time she did not feel well, and noticed progressive weakness and pallor March 3 she had a chill, followed by fever, which lasted several days She did not know what her temperature had been from then until her admission, however, she had been confined to bed all of the time Subsequent to March 6 she had noticed a progressive, dull, aching pain in the left upper abdominal quadrant, which was not present constantly, but, when present, was aggravated by deep inspiration The weakness and dyspnea had progressed until she was completely invalided She had lost much of her appetite, and had been very thirsty There were no gastro-intestinal

symptoms, with the exception of slight constipation which was easily controlled by the use of mineral oil Prior to her admission she had been treated with liver extract and had had a course of roentgen treatment over the spleen Subsequent to March she had passed urine about twice nightly however she complained of no other urinary symptoms.

The patient s weight was found to be about 10 pounds (4 kg) less than usual. Systolic blood pressure was 120 in millimeters of mercury and diastolic pressure 80 the pulse rate was 130 beats each minute and the temperature was 101 F Pallor dyspnea and weakness were marked The entire abdomen was somewhat tender but the left upper quadrant more markedly so than other parts. A large firm tumor seemed to occupy the entire upper left quadrant otherwise, physical examination was negative The urine contained a slight amount of albumin and a few leukocytes. The concentration of hemoglobin was considerably less than normal erythrocytes numbered 3 830 000 and leukocytes 16 900 in each cubic millimeter of blood Roentgenograms of the thorax gave evidence of a thickened pleura with a small amount of fluid at the left base An intravenous urogram indicated that the right renal pelvis calices and ureter were normal but that the left ureter and renal pelvis were displaced mesially and lay adjacent to the spinal column The urologic diagnosis based on this pyelogram was indeterminate left renal tumor Then a retrograde pyelogram was made which disclosed that the left calices, pelvis and ureter were normal. There was no evidence of tumor in the left kidney itself

June 6 1932 exploration was made through a small left lumbar incision a paranephritic abscess was found and about 500 c c. of very foul smelling pus was drained from the region posterior to the left kidney Immediately after drainage of the abscess the temperature returned to normal where it remained throughout the patient s stay in hospital Her convalescence was apparently satisfactory and she was dismissed on the twenty four day after operation

The patient returned July 18 1932 because she had not regained as much strength as she thought she should and because a moderate amount of pus was still draining from the sinus. For a day or two her temperature had been as high as 101 or 102 F Leukocytes numbered 10 000 in each cubic millimeter of blood An intravenous urogram gave evidence that the kidneys ureters and bladder were normal but that there was a mass in the region of the previous paranephritic abscess the outline of the psoas muscle was retained on the left side Retrograde cystoscopy of the left side indicated that the left kidney was normal but was displaced toward the spinal column It was felt at that time that the fever and general condition of the patient were the result of inadequate drainage and some consequent accumulations of pus Accordingly she was sent to the hospital with the idea of effecting more complete drainage. The external opening of the sinus was made larger and a large amount of necrotic-appearing material which resembled carcinomatous tissue was removed. Further exploration disclosed that this tissue extended into the splenic flexure of the colon The surgical diagnosis was carcinoma of the colon The pathologic report of the tissue removed from the kidney was adenocarcinoma graded 2

The interesting feature of both of these cases is that in neither were there symptoms referable to the colon, other than constipation Moreover, in neither case was the constipation bothersome enough to warrant investigation of the colon

An inference to be drawn from this experience is that if surgical drainage of a paranephritic abscess has been effected, and if material continues to drain longer than seems reasonable, the patient's condition meanwhile failing to improve, one should, among other conditions, consider the presence of a carcinoma of the colon, especially if the abscess was on the left side

COMMENT BY HUGH CABOT

In considering massive retroperitoneal infections I think it of some importance to distinguish between those which should be properly called "perinephritic" and those which should be called "paranephritic" Such a distinction has a true anatomic basis and will considerably simplify the problem of treatment

I believe that the word perinephritic, when applied to suppuration, should be confined to those processes which occur in the perinephritic space, which lies between the true capsule of the kidney on the inner side and the perinephritic fascia which surrounds the fat capsule on the outside This fascia is often referred to as the fascia of Gerota and also as the fascia of Zuckerkandl It is a very real structure which is readily appreciated whenever nephrectomy is done since it must be divided before the fat capsule can be exposed It varies somewhat in development but is always a definite and often a strong fascia Within this fascia will be confined, at least for a considerable period, all suppurative processes having their origin within the kidney but which have broken through the true capsule of that organ This enables one to classify together (1) The perirenal inflammation of so-called chronic perinephritis, a lesion particularly common in all chronic suppuration of the kidney and particularly those of the pyelonephritic type, and (2) true perinephritic abscess which comprises those cases in which active suppuration rather than chronic inflammation has developed

Using this definition, perinephritic abscesses will, in 75 per

cent of the cases, be found to be due to hematogenous infection of the kidney generally with the Staphylococcus aureus causing cortical abscesses which coalesce and form a massive abscess, at first this abscess develops within the perirenal fascia but at a later date breaks through The remainder of the cases, which should be properly classified as perinephritic abscesses, are secondary to some gross lesion of the kidney such as pyonephrosis with stone, pyonephrosis without stone, and tuberculosis of the kidney of the pyonephrotic type In all such the lesion has broken its way through the cortex of the kidney and perforated into the perinephritic space In rare cases traumatic rupture of the kidney will form the so-called false hydronephrosis which is in fact a pouring out of urine from the kidney into this space

The term "paranephritic abscess" should be used to describe cases of massive suppuration in the region of the kidney but which originated outside of the perinephritic fascia from some other neighboring structure having access to the retroperitoneal space These abscesses are most commonly due to lesions of the colon, of the vertebræ, whether from the body or from the transverse process, and occasionally from some suppurative process originating in the liver, particularly on the under surface of the right lobe

The foregoing classification is helpful in diagnosis and treatment in the following ways With true perinephritic abscess there is often a history of some suppurative process on the surface of the body, such as boils and carbuncles, not rarely of recent sore throat, and occasionally of osteomyelitis In the absence of a previous gross lesion of the kidney, such as pyonephrosis of the types described, the urine will be practically normal although in the early stages staphylococci may be found in abundance For some obscure reason they are rarely associated with extensive renal injury, perhaps because the cases of more severe metastatic infection of the kidney go on to destruction of the kidney before the perinephritic abscess has time to develop Whatever may be the cause it is certainly the rule that true perinephritic abscess will develop from a relatively uninjured kidney, and drainage of this abscess will result in cure

Exceptions to this rule lie in those cases in which there is a gross lesion of the kidney which can readily be demonstrated by modern methods of urologic study If the kidney is apparently normal, the abscess will heal after satisfactory drainage without leaving a sinus In cases due to rupture of the kidney from gross renal lesions, nephrectomy will, as a rule, ultimately be required and in many cases a persistent and generally a urinary sinus will result from drainage

Now, in the case of paranephritic suppuration, the case is quite different Study of the kidney will show it to be normal, but drainage of the abscess will rarely be followed by healing since it does not attack the origin of the suppuration which will continue to keep up a persistent sinus Thus in the cases which originate from the colon or from the vertebral column a persistent sinus is to be expected and its cure will depend on the possibility of dealing with the underlying lesion satisfactorily

If the anatomic facts I have suggested are borne in mind, it will as a rule be possible to distinguish either before or at the time of operation between these abscesses which should be classified as perinephritic and those which are paranephritic, thus enabling a more satisfactory plan to be made for comprehensive treatment

DIAGNOSIS AND TREATMENT OF CERTAIN TYPES OF COLITIS AND SO-CALLED COLITIS*

PHILIP W BROWN

The resounding diagnostic term, "colitis," which now covers a multitude of abdominal diagnoses, both actual and pseudo, will doubtless bring smiles to the faces of future physicians, just as physicians now smile kindly but rather patronizingly at diagnostic terms of a past era, such as "liver trouble or bilious ness" Although one would not now suggest such a vague diagnosis as "liver trouble" nevertheless it is simple, satisfying and one might say, lucrative, to say, "Yes, you have colitis!" Any vague abdominal complaint, gas, constipation, diarrhea, and so forth, may all be swept into the heap of "colitis" Such practice has served greatly to confuse the diagnosis and treatment of true colitis, as well as the treatment of the much larger group of cases which remain in the scrap basket diagnosis of colitis

I have recommended that the term, colitis, be reserved for those cases in which actual inflammation of the colon can be demonstrated by the roentgenogram or the sigmoidoscope On this basis then the types of the condition most frequently ob served in the Northwest are amebic colitis, chronic ulcerative colitis, and tuberculous colitis Rarely, one may recognize colitis due to Balantidium coli Proctitis due to radium reaction, gonorrheal infection, improper irrigating solutions, and so forth is not uncommon, but the history of the case and the limitation of the disease to the lower 24 to 30 cm of the bowel should serve to diagnose these types correctly Recently the tendency has been to minimize the possibility of syphilis as a cause of

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ulceration or stricture in the rectum and colon I feel that this is consistent for cases from rural centers, but in city dispensaries it is probable that both gonorrheal and syphilitic lesions of the rectum and colon are encountered more frequently

TUBERCULOUS COLITIS

The type of disease of the colon, due to the bacillus of tuberculosis, determines whether the treatment should be medical or surgical

In active pulmonary tuberculosis,[4] enterocolitis due to tuberculosis is a common complication although tuberculous peritonitis is a rare complication Any digestive disturbances, failure to gain weight, or irregular fever, are suggestive of intestinal complication In more than 50 per cent of postmortem examinations of patients who have died of pulmonary tuberculosis intestinal tuberculosis is found

There is a more chronic type of tuberculous colitis, usually secondary to low grade or quiescent tuberculosis elsewhere in the body It involves chiefly the right half of the colon This part of the bowel is thickened, the lumen is narrowed, and the process tends to terminate gradually in the transverse colon Usually the terminal ileum is also involved In such cases diarrhea is the most common but seldom severe symptom, usually three or four stools daily The stools are likely to be mushy and may show gross evidences of pus but rarely of blood It is only when the tuberculous lesion approaches the rectum that blood may be seen by the patient There are usually complaints of gas, mild to moderate cramps, and gradual decline in general health but not so marked as in the cases of enterocolitis in which involvement of the bowel is essentially a terminal phenomenon

Examination of the stools will reveal pus, and usually blood, if the specimen is stained, the bacillus of tuberculosis may occasionally be identified Whether this bacillus is swallowed or actually comes from the ulcerated bowel must be considered Results of examination by the sigmoidoscope will be reported negative unless the disease has progressed to the rectum On roentgenologic examination the long segment of involved bowel,

the absence of jagged appearances of the margins of the involved segment, and the tendency of the process to terminate gradually will usually serve to establish the diagnosis It is a fairly safe working rule that tuberculosis usually begins in the ileocecal area and progresses caudad, whereas the reverse is true in 90 per cent of cases of chronic ulcerative colitis The roentgenogram of the thorax is an essential part of the examination, although there are infrequent instances of tuberculous colitis without clinical evidence of pulmonary tuberculosis

Another type of the disease is the tuberculoma or localized hyperplastic lesion This type tends to manifest itself by producing gradually increasing obstruction of the bowel The most common site for the tuberculoma is the ileocecal coil The lesion may be single or there may be other tuberculomas in various parts of the colon and small intestine In view of the obstructive tendency of tuberculomas, W J Mayo, years ago, advocated surgical resection as the method of choice, or if this is not feasible, short-circuiting around the obstructed areas

The incidence and type of primary intestinal tuberculosis is frequently questioned The former teachings of the high percentage of anal fistulas due to tuberculosis may be recalled Several years ago I reviewed a group of thirty two cases of tuberculoma of the bowel[5] and in ten a focus of tuberculosis outside the intestine could not be demonstrated, nor could the possibility of a latent focus in the nodes of mesentery or hilum be disproved I suggested that this group of ten cases might represent primary intestinal tuberculosis and further that infection might be caused by infected cow's milk

There is no question that anorectal tuberculosis occurs, we are all familiar with the scarred buttocks, multiple sinuses, and inflamed rectal mucosa of some of these patients Buie found an incidence of tuberculosis in anal fistula of 0 27 per cent of 1,000 cases This should represent a fairly accurate cross section of the average population, although it may naturally be less than in cases observed in a tuberculosis sanitarium

The treatment of enterocolitis and colitis is still unsatisfactory The usual measures for pulmonary disease, as carried

out in the sanitarium, seem the best The diet should be of the smooth, bland type, making sure that ample vitamins are provided Calcium, orally, may help and is given in 4 gm doses of calcium lactate three hours after meals Kline advocated giving the calcium in conjunction with capsules of soricin (sodium ricineolate), one capsule half an hour before meals, with cold water Roentgenotherapy has been advocated but is of uncertain value, it should be used cautiously, as we know the irritating effect of the roentgen rays on the bowel Colonic irrigations are probably of no more value in tuberculosis than in any other intestinal disease

The prognosis of enterocolitis as a complication of pulmonary tuberculosis usually is grave In more chronic colitis, the outlook is somewhat more cheerful With the tuberculomas, the number of lesions and the type of operation possible determine the ultimate outcome

CHRONIC ULCERATIVE COLITIS

Although the etiology of chronic ulcerative colitis is still questioned, I believe that it may be attributed to the diplococcus isolated by Bargen [3] There is a recurrence of opinion that the organisms of bacillary dysentery, explain this chronic disease Undoubtedly certain cases of chronic bacillary dysentery do occur but in the type considered as chronic ulcerative colitis, the organisms of dysentery are not the offending ones Years ago, antidysentery serum was tried at the clinic in several cases of chronic ulcerative colitis, with no improvement In 1931, Bargen, Copeland, and Buie reported a most careful study in fifty-six consecutive cases of chronic ulcerative colitis Agglutinins for the dysentery group were sought in the blood serum and cultures made directly from the rectal ulcerations were examined for the bacillus of dysentery, the results were entirely negative for evidence of the bacillus

Chronic ulcerative colitis is characterized by its chronicity, its remissions, and its tendency to involve the entire colon Further, the disease usually starts in the rectum and extends back to the ileocecal valve Years ago, Logan noted a similarity

between chronic ulcerative colitis and duodenal ulcer, in that both manifested periods of activity, to be followed by remissions, often irrespective of treatment Finally, in many instances, these diseases would settle down to a steady, chronic grind

Acute intercurrent respiratory infection, or acute diarrhea resulting either from intercurrent infection or infected food may initiate the first chapter of this distressing disease. The stools will vary in number, depending on the severity and amount of colon involved, blood and pus are noted, and often the stool consists of little else than "bloody, slimy, stuff" If the activity is chiefly above the region of the rectosigmoid, or if it is more in the right half of the colon, there may be only three to five stools a day, whereas with active ulceration of the lower left half of the colon there may be twenty to thirty or more stools in twenty-four hours The initial attack may last only a few days and then subside Gradually the attacks recur more frequently and last longer Slowly the entire colon tends to become involved, although in an occasional case, the patient's resistance may not prevent recurrence and yet will limit the progress of the disease

Examination of the stools will not reveal anything of positive value in making a diagnosis except that from them, it is usually possible to culture and isolate the diplococcus On sigmoidoscopic examination, the diffuse, granular, easily bleeding mucosa is highly characteristic The primary ulcerations of chronic ulcerative colitis are the tiny miliary ulcers which later break down to form the disseminated, shaggy, larger ulcers of the secondary type There may be more or less contraction of the rectal lumen On roentgenologic examination, the filling defect is usually long, the margin of the canal tends to be smooth, and the wall, although obviously thickened, remains pliable Hyperirritability of the involved segment is usually a prominent feature In extreme cases, the narrow, shortened colon, scarcely more than a small, stiff tube, is found Less frequently, segmental areas of ulcerative colitis may be found and the differential diagnosis of tuberculoma, carcinoma, and colitis is not always simple

The complications of chronic ulcerative colitis may influence

the final picture, arthritis, perirectal infection, severe secondary anemia, polyposis, and superimposed malignancy of the bowel all add to the problem of diagnosis and treatment

Treatment of chronic ulcerative colitis, as outlined by Bargen[1] consists of (1) Immunization, vaccination or desensitization against the diplostreptococcus of ulcerative colitis, (2) removal of all distant foci of infection, and (3) a liberal, high vitamin diet This is accomplished by administering to patients who are less severely ill, vaccines prepared from the diplostreptococcus isolated from rectal lesions of patients with the disease, and to patients who are more severely ill, a specific antibody solution (concentrated serum) prepared by immunization of horses All demonstrable foci of infection should be eradicated as far as possible Teeth with periapical abscesses, infected tonsils, and even tonsils that are suspected of being infected should be removed Prostatic infection is difficult to treat in these cases and probably should not be tampered with What the patients should eat varies with the severity of the disease Little digestion takes place in the large intestine, and unquestionably too much dietary limitation has been practiced in the past Diet for the ambulatory patients, as employed at the clinic, consists of 3,000 calories of foods of high-calorie value and relatively low residue Attention is paid to an adequately balanced ration of vitamins This diet will be varied in accordance with the activity of the disease At times it has to be initiated by the administration of liquids only, but even these should be high in calories Many of the patients tolerate milk poorly Therefore this is added to the diet only when patients, who have previously limited their diet, often to extreme degrees, begin to relish their food

Symptomatic treatment with occasional rectal irrigations with hot saline solution, the administration of opiates, hot abdominal stupes, and so forth, are often of much help The various powders are seldom of much value Tincture of iodine in 10-drop doses well diluted, after meals for one week each month, has seemed of some value Rarely, in a typical case of chronic ulcerative colitis the patient will be much improved by the ad-

ministration orally of stovarsal, but this or any other arsenical must be given with great caution as it may not only cause acute exacerbation of the colitis but may produce arsenical poisoning I have tried many solutions for irrigating the colon and have decided that with the exception of a gently administered, warm saline solution, none is of much value, the only value of the saline irrigation is to rid the rectum temporarily of irritating secretions and afford some local comfort by the warmth of the solution

With the advent of certain complications, operative procedures must be considered Ileostomy is preferable to appendicostomy It should not be undertaken in the acute fulminating case, since medical treatment offers as good or better chance for cure Strictures of the colon and rectum, polyposis, and some of the more severe perirectal infections are among the common indications for ileostomy It should always be borne in mind that ileostomy is usually permanent. In rare instances, ileosigmoidostomy may later be possible, but the operation is attended with a high mortality and a high incidence of extension of the colitis into the ileum, as a result of the tendency to exacerbation of the disease in the rectal stump Now when ileostomy is performed, plans are made later to perform colectomy and resection of the rectal stump, a long, expensive and dangerous procedure and hence to be undertaken only after careful and repeated consultations

AMEBIC COLITIS

Craig estimated that between 5 and 10 per cent of persons in this country harbor Endamœba histolytica Undoubtedly this parasite is being recognized more frequently in recent years in the North Temperate Zone [1] recently reviewed experience in The Mayo Clinic of the last ten years, and concluded that although amebiasis is certainly present throughout the continent, yet the incidence, as well as the severity of the disease, seems less marked in northern than in southern regions

The parasite may produce gross ulceration of the colon, which is most marked in the cecum and rectum. Occasionally,

the ameba is swept to the liver through the portal circulation and sets up hepatitis, or amebic abscess of the liver This abscess may rupture externally or into the right side of the thorax, with resultant symptoms, almost entirely pulmonary Rarely the parasite may migrate to the brain or spleen Involvement of the skin is recognized and is usually secondary to a draining amebic sinus I do not believe that Endamœba histolytica is a cause of iritis, arthritis, or eczematoid dermatitis Furthermore, this parasite is not likely to be the cause of a patient's complaint unless diarrhea or abscess is associated I urge eradication of the ameba in any case in which it is found but in the absence of the active symptoms described, it should be explained to the patient that the treatment may not result in benefit of the complaints, but it will protect against a possible attack of amebic colitis or abscess of the liver as well as prevent him from spreading the infection

The diagnosis is made on the identification of the parasite from a freshly passed stool, from swabbings of a rectal ulcer, or from a draining sinus On visualizing the rectal mucosa, the punched-out ulcer with normal intervening mucosa is all but pathognomonic On roentgenologic examination, the colon may appear normal or may show narrowing and spasm which simulates chronic ulcerative colitis Usually, the most active involvement is in the cecum, which should at once suggest amebic colitis The terminal ileum is not involved and hence is a point in the distinction from tuberculosis

The treatment which I have found satisfactory is the administration of emetine hydrochloride and treparsol Emetine is spectacular in controlling acute symptoms, and an organic arsenical, such as treparsol, is more effective in ultimately eradicating the parasite

Emetine is administered hypodermically in doses of $\frac{2}{3}$ to 1 grain (0 043 to 0 065 gm) twice daily for three days At the same time treparsol is administered orally in 0 25 gm tablets with each meal for four days After an interval of a week, the course of emetine is repeated A rest period of eight to ten days is essential before repetition of treparsol course Two

courses of emetine and three of treparsol apparently will effect cure in 90 per cent of the milder cases and in fully 60 per cent of the severe cases In the treatment of carriers, treparsol alone is sufficient in fully 90 per cent of the cases

In cases of recurrence, or if the patient has recently had an unknown amount of emetine or arsenic, yatren (anayodin, chiniofon) is prescribed This drug is given orally in doses of 1 gm after meals for a week and repeated for two more such courses allowing a rest period of one week between courses In amebic abscesses of the liver the emetine and treparsol regimen is combined with as conservative a surgical procedure as is possible, preferably aspiration only

As emetine and arsenic are definite poisons, care must be taken to watch for any untoward symptoms, and treatment should be strictly supervised However, hospitalization is unnecessary, unless the patient is very ill

INDETERMINATE DIARRHEAS AND SO-CALLED COLITIS

As fully two-thirds of all cases of diarrhea do not fall into the foregoing main types of true colitis, or into other less common varieties, this larger group taxes the ingenuity of the conscientious physician and constitutes a generous part of the clientele of the "food faddist" and the "colon irrigator" These patients visit various sanatoriums, medical centers, and clinics, hoping ultimately to find a cure for their mucous colitis, spastic colitis, or just colitis In reality, the physician who gave the patient these diagnoses should be sought for, not to wreak vengeance on him, but to point out that these disturbances in colonic function are not diseases of the bowel but secondary to nervous, dietary, allergic, or reflex factors Not until the patient can be made to realize that the function and not the structure of the colon is altered, will progress be made in relieving his distress Acute intercurrent infections, probably streptococcal or staphylococcal in origin, seldom are associated with colitis, they are usually short lived and tend to terminate spontaneously This is also true in cases of dysentery, although in some epidemics,

there is a fairly high mortality Occasionally, chronic diarrhea follows on the heels of these acute episodes

It is beyond the scope of this paper to more than mention some of the commoner types "Irritable colon" refers to a condition of intermittent or steady diarrhea, and often periods of constipation "Reflex diarrhea," produced by disease in the appendix, gallbladder, pelvis, and so forth, is another type Diarrhea due to food allergy is sometimes a definite condition and must always be borne in mind One should be cautious about making a too prompt diagnosis of allergy, as this particular field is likely to become unduly exploited

A form of diarrhea difficult to cure apparently results from dietary deficiency The condition varies from mild to a more severe type, which strongly resembles sprue One may be confused in making a diagnosis by the presence of fat in the stool and consider whether it is due to a deficiency diet, or to faulty digestion of fat, probably pancreatic in origin, which rarely occurs

Finally, the most trying form of chronic diarrhea is the purely neurogenic type In other types the functional phases are often in the foreground and it is always essential to recognize this feature Certainly it is this large group of neurotic patients who need wise counsel so much more than they need a specialist

I should like to call attention to the relative infrequency of achlorhydria as a cause of diarrhea About 10 per cent of such patients have diarrhea and only a few of them note any benefit by the taking of hydrochloric acid Hydrochloric acid should certainly be tried, but if the response is not prompt, further study and treatment must be carried out

The treatment[7] previously suggested, of these various forms of chronic diarrhea may be summarized as follows

1 A well-assorted, adequate diet, administered as rapidly as is consistent with the patient's tolerance, is the goal to be achieved for chronic diarrhea of unknown origin It is, of course, impossible to prescribe a diet which is suitable in all cases Far more harm is done by a too limited diet than by a too free diet Many patients have been on such a restricted diet that it is absurd to

assume that they can take care of much food at first At the onset the patient may fear to eat because of former restrictions and the fear that disastrous results may ensue I suggest a diet low in residue in the beginning, which includes 60 to 120 gm of meat, 15 c.c of purée of vegetables in milk soup, and also a purée of vegetables in meat soup In this primary diet an effort is made to incorporate as many foods as seem to agree with the patient The foods are gradually increased, adding slowly the stewed fruits and vegetables Finally, raw fruits and vegetables may be added Individual variations are, of course, necessary, especially in the presence of allergy Occasionally it is necessary to supplement the diet with proprietary concentrates of vitamins B and D If the digestion of fat is faulty, the diet best tolerated is usually low in fat, fairly high in protein, and rich in carbohydrate. In cases of sprue, raw liver or its equivalent is included and gradually decreased as the patient's condition improves The carbohydrates must usually be kept low as the patients' tolerance to them is poor One patient had a rather long siege on a diet of protein and orange juice, but is finally on a full normal diet

2 Irrigation of the colon has little if any place in the treatment of diarrhea The occasional use of a small, warm saline enema, preferably at bedtime, may be of aid, but its constant usage is not advisable If the bowel is irritable, especially if diarrhea alternates with constipation, small oil retention enemas may be used temporarily

3 Drugs are of uncertain value. I question the value of inert powders, as they seem in many cases merely to add to the material which must be excreted Tincture of belladonna is also of doubtful value Occasionally a dramatic response may result from the use of 6 grains of emetine hydrochloride hypodermically, but in such a case I think the result must be ascribed to the specific action of emetine on an undiscovered infection by Endamœba histolytica In the types of diarrhea considered in this paper, emetine has no effect Organic arsenicals, as treparsol, may be worthy of trial and infrequently seem to be beneficial. The benefit is probably on a nonspecific basis A

new product that may prove of value in some cases is 2-4-dihydroxyphenyl n-heptane (dihydranol) I have tried it in the postinfectious type of diarrhea and it seemed to be of value in two cases In the sprue-type of diarrhea and to a less extent in the allergic type, calcium lactate in large doses over a long period has seemed useful In some instances, I have used it with parathyroid medication Tincture of iodine by mouth in doses of 10 drops after meals, well diluted, has occasionally helped and is worth bearing in mind Mild sedative drugs play a helpful part and judicious usage is made of bromides or the barbital group

4 Vaccine treatment in irritable and allergic conditions of the bowel has received considerable impetus by the work of Dorst and Morris During the last two years, several patients have been treated according to this method An adequate diet was outlined and nonspecific drugs were usually included, such as iron citrate for the anemia and calcium lactate Sorcin, orally, was included with the vaccine treatment

My initial impression is not especially favorable to treatment by vaccine in most cases of indeterminate diarrhea McCarrison's experimental work may be applied to human beings in that inadequate or deficient diet can so lower the functional perfection of the gastro-intestinal tract as to impair its natural immunity to the customary organisms of the colon Whether treatment by vaccine is the approach to restoring this resistance is a matter to be determined

SUMMARY

Some of the essential points in the diagnosis and treatment of derangements of the bowel due to tuberculosis, chronic ulcerative colitis, infection from Endamœba histolytica, and more briefly, some of the indeterminate types of chronic diarrhea, have been considered

The term "colitis" should be reserved solely for conditions in which there is demonstrable inflammation of the colon

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A CLINIC FROM THE COLON SERVICE

PHILIP W BROWN AND ROBERT L HARGRAVE

Case I.—A woman first came to the clinic in January 1923 when she was fifty five years of age. She then complained of gradually increasing constipation to which had recently been added attacks of actual obstruction In addition she gave a history of periodic attacks of epigastric pain relieved by taking of food or soda. The diagnosis of carcinoma of the descending colon was established and successful Mikulicz resection was performed by Pemberton

The patient has been examined at frequent intervals She visited the clinic in 1925 when it was possible to investigate the gastric condition and a diagnosis of duodenal ulcer was made. Her general health remained good except for some distress from the ulcer there was no evidence of recurrence of the intestinal carcinoma

In September 1932 she was sixty five years of age and while she was visiting relatives she committed dietary indiscretions September 12 she complained of malaise weakness, nausea and sweating These manifestations recurred in the evening of that day and she vomited a large amount of black, tarry material Following this she fainted and thereafter tarry vomitus as well as tarry stools persisted for several days. September 22 she was taken to a hospital where the stomach was examined roentgenologically and a diagnosis of duodenal ulcer was made again She decided to return to the clinic, and arrived here September 26

She was rather obese and was pale The abdomen was definitely distended and tympanitic. A firm full smooth mass was palpable in the left side of the abdomen just beneath the site of the previous intestinal resection The value for hemoglobin was 6 48 gm in each 100 c.c. of blood erythrocytes numbered 2,310 000 and leukocytes 3 900 in each cubic millimeter of blood There was no fever

In view of the partial intestinal obstruction as well as the patient's generally weakened condition studies of the intestine were not indicated It was probable that at least some of the mass in the left side of the abdomen was due to accumulation of barium given orally four days previous to her admission Following a series of colonic irrigations and hot abdominal stupes, the abdomen became softer and barium was expelled October 3 the abdomen was soft although a rounded mass persisted in the region of the scar A barium enema revealed a large intraluminal mass (Fig 214) proximal to the site of the fomer resection The following day a small amount of bar

ium was given orally, and this examination confirmed the former diagnosis of duodenal ulcer

Clinically, the signs pointed to the diagnosis of fecolith, but persistent irrigations, retention oil enemas, and oil given orally, in conjunction with a diet low in residue failed to reduce the mass, which was about 10 cm in diameter However, since the possibility of recurrence of the carcinoma was not entirely excluded, and also since the fecolith would present a constant threat of obstruction at the narrowed site of anastomosis, Pemberton again explored

Fig 214 —Fecolith at site of anastomosis Mottled, round appearance may be noted

the abdomen October 13 No evidence of recurrence of the carcinoma could be demonstrated There was some narrowing at the previous operative site but not enough to warrant resection The colon was opened, and a firm, hard fecolith, 7 cm in diameter, was removed It was a true fecolith and not merely a mass of barium sulphate Convalescence was relatively uneventful, aside from development of a fistula at the operative site This closed spontaneously in about five weeks At the time of the patient's dismissal a bland diet was outlined, and was supplemented by a daily dose of mineral oil

Comment on Case I—This case illustrates the satisfactory result possible (nine and a half year cure) in treatment of carcinoma of the descending colon Although recurrence at the point of resection would be rare after such an interval, yet it was possible, and this fact, together with the presence of the fecolith, was a definite indication for operation It is of interest that the lumen was of fair size at the previous site of resection, and yet enough stasis, or back current, was present to result in fecal concretion

All this had nothing to do with the hemorrhage from the duodenal ulcer It is to be hoped that by care concerning diet and, for the time being, use of alkaline powders, the patient will prevent further activity of the ulcer The bland diet is favorable both to healing of the ulcer and to passage of fecal matter through the narrowed bowel, for in such a diet cellulose is kept at a minimum

Case II.—A woman aged sixty seven years, came to the clinic November 1932 She had been well until 1925 but thereafter had had intermittent attacks of watery diarrhea coming on every two or three weeks and lasting a day or two at a time. The attacks had been followed by periods of constipation during which she had taken mineral oil and agar This condition had continued until *March 1932 at which time she had had an attack of* lower abdominal pain which had lasted a week The pain had been sudden in onset constant and at first had involved the right side but later had localized in the left lower abdominal quadrant and had been associated with fever and vomiting A few days after this attack the patient had manifested evidence of cardiac decompensation with edema of the lower extremities and albuminuria The systolic blood pressure which previously had been 150 mm. of mercury was elevated to 220 The patient was given digitalis, and within three weeks was up and about as usual During this episode there had been some weakness and numbness of the right arm and left hand which had disappeared after a week or so After March the attacks of diarrhea had been more severe, and had lasted six or seven days at a time. At no time had blood pus or mucus been noticed in the stools In addition there had been rumbling noises in the abdomen and diffuse, cramping pains throughout the abdomen but chiefly in the lower quadrants. The appetite had been poor and the patient had lost 50 pounds (about 23 kg) She had been troubled with some vomiting for a few days prior to her admission

The patient was moderately obese even though she had lost 50 pounds. The systolic blood pressure was 140 and the diastolic 58 The pulse rate and the temperature were normal There was some question of diminution of the breath sounds over the base of the left lung posteriorly The heart was

somewhat enlarged, and there was a blowing systolic murmur over the aortic and mitral areas The abdomen was moderately distended, and a tender mass, about 10 cm in diameter, could be felt in the left lower abdominal quadrant There was slight edema of the ankles Nothing significant could be felt through the rectum The urine contained a trace of albumin, a few hyaline casts, and a few pus cells The value for hemoglobin was 15 4 gm for each 100 c c of blood Erythrocytes numbered 4,780,000 and leukocytes 9,800 in each cubic millimeter of blood Flocculation tests for syphilis were negative The value for urea was 20 mg for each 100 c c of blood In the electrocardiogram there was a diphasic T wave in derivations 1 and 2, a notched P wave in derivations 2 and 3, a diphasic P wave in derivation 3, and a slurred QRS complex in derivations 1, 2, and 3 Roentgenograms of the thorax gave negative results, except for evidence of a tortuous aorta Proctoscopic examination disclosed questionable diverticula of the sigmoid Roentgenographic examination of the colon, after barium enema, disclosed an obstructing lesion of the sigmoid, probably carcinomatous, with considerable dilatation of the colon proximal to the lesion Because of the absence of blood in the stools, and because of the long history, the question arose whether the condition might not be diverticulitis, although the most probable lesion was a carcinoma

The patient was admitted to the hospital November 15, 1932 The abdomen was only slightly distended, but in attempting to give antiperitonitis vaccine intraperitoneally, a loop of bowel was punctured, evidence of which was clearly shown by the escape of gas and fecal material from the needle The needle was immediately withdrawn No evidence of peritoneal irritation followed the incident The patient was operated on November 17, 1932, under spinal anesthesia. A small, high, left rectus incision was made, and the abdomen was explored An obstructing lesion was found 8 to 10 inches (20 to 25 cm) from the rectosigmoid juncture Colostomy was performed, employing a loop of transverse colon The colon was markedly dilated proximal to the obstruction Following the operation, sudden cardiac decompensation developed, with auricular fibrillation, and the patient died the following morning

Comment on Case II—The long history of intestinal dysfunction, with both obstruction and diarrhea, should have suggested that the condition was the result of inflammation rather than of neoplasm Of course, at this time, the obstruction was rapidly increasing, and although it was not complete, it was apparent that it would soon be so In addition, there was the added risk of myocardial degeneration The decompensation and the subsequent lowered blood pressure were sufficient proof of the presence of an imperfect heart This is the type of case in which the surgeon realizes that the odds are greatly against a successful outcome, but it is a responsibility which he cannot

avoid, in this case the patient succumbed twenty hours after operation, because of cardiac failure

The specimen of the bowel obtained at necropsy contained the localized stricture caused by diverticulitis (Fig 215) The dilatation of the proximal part of the bowel was apparent, and left no doubt that operation was necessary

Fig 215.—Stricture of sigmoid due to localized diverticulitis. Relatively normal mucosa at site of stricture and marked dilatation of proximal part of colon may be noted

The apparent puncture of the bowel in the course of intraperitoneal vaccination is of interest in that infection did not result, as was proved by necropsy Such an accident is very rare in a series of many hundred such vaccinations but demonstrates that a sterile needle puncture of the bowel is not likely to be followed by trouble

Case III.—A man aged fifty-one years, registered at the clinic October 14 1932 For fifteen or twenty years prior to 1921 he had been markedly constipated and from time to time had taken purgatives and laxatives in order to get cleaned out He had felt run down for a year or two previous to 1921 In 1921 severe abdominal pain developed localized to the left lower abdominal quadrant and this was attended by high fever and numerous convulsions, which lasted for about two weeks. A tender tumor appeared in the left lower part of the abdomen. The condition at first had been called

carcinoma and later, diverticulitis and mucous colitis Five days after the onset of the abdominal pain a large abscess ruptured into the bowel, and much pus was passed by rectum for the following two or three months Six weeks after the onset of his trouble, the patient passed a black, cylindrical object about 4 inches (10 cm) long, which resembled a bicycle tire tube more than anything else He was confined to bed for ten weeks but was not completely well until a year and a half later Since 1921 he had taken mineral oil and milk of magnesia to keep his bowels open At times he had felt well, at other times, run down For about ten months before registering at the clinic he had occasionally noticed in the right midabdominal region a few sharp, shooting, crampy pains not unlike those caused by a "bubble of gas" He had been working hard, and for three or four months prior to registration had felt much run down, this, he believed, might explain his abdominal cramps The appendix had been removed in 1913

The man was small and thin The abdomen was essentially normal, except for slight tenderness in the left lower quadrant The reflexes were normal as were, also, the urine and blood The Kline and Kahn tests were weakly positive Roentgenograms of the thorax revealed evidence of an old, healed tuberculous process, involving the upper lobes of both lungs Proctoscopic examination gave negative results Roentgenographic examination of the colon with barium enema disclosed a lesion of the hepatic flexure, characterized by multiple polypoid masses with a tendency to intussusception A diagnosis of probable polypoid carcinoma was made

At operation a multilobular submucous lipoma, 6 by 7 by 5 cm in diameter, involving the ascending colon at the hepatic flexure, was found The tumor was brought out on the abdominal wall as part of a Mikulicz operation, and was subsequently removed with cautery Postoperative convalescence has been uneventful

Comment on Case III —Benign tumors of the large bowel are rare Because we consider all adenomatous polyps of the bowel as potentially or actually malignant, lipomas are the most common benign lesions Myomas, fibromas, and angiomas are less common, and are found in decreasing frequency in the order noted Their presence is seldom suspected until they produce mechanical occlusion of the lumen, or until, by extrusion, they produce intussusception or volvulus Blood in the stools is noted rather frequently in lipomas and is due to the mucosa overlying the tumor becoming ulcerated In such cases, the presence of melena will suggest the probability of carcinoma Of course, surgical intervention is indicated in either case, and undue delay would be unwise

Roentgenograms (Fig 216) aid in establishing the presence of an obstructing lesion probably due to a polypoid tumor Mild

symptoms of obstruction were developing, and fairly surely definite blockage eventually would have occurred Since the lesion proved to be benign there need have been no hurry in

Fig 216—Lipoma of hepatic flexure. Lobulated patchy appearance of the tumor may be noted

operating, but it was much easier and safer to perform the resection while the patient was in good condition and was not having actual obstruction

Case IV—A man aged twenty-seven years, was admitted to the hospital October 16 1932 The previous spring he had received rectal injections for hemorrhoids and he said that abscesses in the rectum had subsequently developed The abscesses were opened and finally an operation was performed under ether anesthesia The man was under treatment for the next two months, at the end of which time the rectal condition had completely subsided Following this, the patient was well until the first part of

September, when cramping pains developed in the abdomen, and three or four loose, watery stools were passed each day Four weeks before admission to the hospital, fever began to appear in the afternoon, then loss of appetite and general malaise appeared, and the number of movements of the bowels increased to four to six each day Three weeks before admission the man began to pass blood by rectum At times there was much bleeding, and often large clots were passed Bleeding had been excessive for two or three days before admission In addition to the blood, there was much pus and mucus in the stool His afternoon temperature was between 102° and 104° F and he experienced further loss of appetite, some loss of weight, and marked weakness Pain in the abdomen was a prominent symptom, and he had been confined to bed since the onset of the rectal bleeding Agglutination tests for typhoid fever and Malta fever performed at his home had been negative.

The patient was well developed and even slightly obese. He looked ill and his skin was pale and moist The pulse rate was 128 beats each minute, and the temperature 101 8° F The abdomen was distended, doughy, and slightly tender along the left side The anus was too tender to permit of satisfactory examination, other than be sure that a rectal tumor was not present A tentative diagnosis of acute ulcerative colitis was made. The value for hemoglobin was 9 12 gm for each 100 c c of blood, erythrocytes numbered 3,410,000, and leukocytes 12,100 in each cubic millimeter of blood The value for urea was 20 mg in each 100 c c Flocculation tests for syphilis were negative The urine was essentially negative, except for a trace of albumin Examinations of stools on four consecutive days were negative for ova, parasites, bacilli of tuberculosis, and the diplostreptococcus of chronic ulcerative colitis

From October 17 to 20, the patient received daily intramuscular injections of chronic ulcerative colitis serum, beginning with 0 1 c c. and increasing each subsequent dose by 0 2 c c. Proctoscopic examination, October 19, disclosed several ulcerations on the mucous membrane, just above the dentate margin, with a draining sinus on the right side 3 cm above the anus and a similar sinus on the right anterior wall of the rectum The rectum and rectosigmoid were otherwise normal

October 20, 500 c c of citrated blood were given intravenously This measure was repeated October 23 The number of stools averaged two to three each day, and the patient had no further hemorrhage. While he was in the hospital, his pulse rate gradually increased and the temperature ranged between 100° and 102 5° F The abdomen gradually became more distended and the general condition progressively worse The patient became so weak that he had great difficulty in turning over in bed October 21 and 22, he received 1 grain (0 065 gm) of emetine hydrochloride intramuscularly twice daily The distention was now chiefly in the upper part of the abdomen In the following three days his condition became progressively worse, with the pulse rate and temperature rising From the onset, surgical consultants saw no indication for intervention The patient died October 24, eight days after admission

Comment on Case IV.—At postmortem examination it was found that much of the abdominal distention was due to free gas in the peritoneal cavity. There was generalized peritonitis, with a large perforation in the cecum (Fig. 217) and several smaller perforations throughout the proximal two-thirds of the colon. The colon was the seat of severe, fulminating ulcerative colitis which was so marked in the cecum and ascending colon

Fig. 217.—Severe perforating and perforated acute ulcerative colitis of the cecum.

that only small strips of mucosa remained. Contrary to the usual features of chronic ulcerative colitis, the disease in this case was most marked on the right side of the colon, the sigmoid and rectum were free of ulceration.

The question arises as to why ileostomy was not performed on the day of admission. Although ileostomy has proved to be a life-saving measure in a few instances, as well as a suitable procedure in treatment of the complications of ulcerative colitis,

our experience of the past few years has led us to feel that the acute phases of the disease are more likely to be controlled by administration of serum and other medical measures than by operation In addition, the patient escapes ileostomy, which is so likely to be followed by permanent ileac stoma In the cases in which recovery does not follow medical treatment, we doubt if surgical operation will offer much In previous work the mortality in similar cases has been almost prohibitive (fully 75 per cent) Necropsy in this case revealed that the colon was nearly destroyed and that a condition which almost might be called diffuse perforation was present, it is scarcely conceivable that operation would have accomplished more than to hasten the unfortunate result

Since the introduction of serum and vaccine, the mortality rate of ulcerative colitis has greatly decreased, and operation has been limited in application almost entirely to complications such as stricture, polyposis, and so forth

NEUROGENIC FACTORS IN PEPTIC ULCER*

HOWARD R HARTMAN

The increasing interest in the neurogenic factors in peptic ulcer has mounted until in the minds of a constantly enlarging circle of proponents there is no doubt of the existence of these factors, but the proponents are in a quandary to know how much importance to give to them Perhaps this is true because no proof is available Opponents admit that there is something to the hypothesis, although antipathy to the idea could well enough be engendered by unwillingness to try to understand the complexities of life and the workings of the autonomic nervous system Those who are practically minded, who want proof in figures, toss the idea aside with some subtle criticism of the observations of gastro-enterologists, but they, although they may not be thoroughly acquainted with neurologic science, are in a position to see ulcer in its broadest aspects They write, not from the viewpoint of the neurologic surgeon, who sees ulcer associated with a lesion of the brain, not from the viewpoint of the endocrinologist nor of the laboratory research worker, but from the viewpoint of the ulcer bearing patient, who is submitted to the bodily insults to which anyone is heir

I do not think that full cognizance has been taken of the importance of neurogenic influences in causing ulcer, nor of the benefit obtained by removing these influences I have no convincing proof other than the convictions of many internists, the observations of intelligent patients who have ulcer, and my firm belief that in some way the nervous system plays a dominant part in the etiology of ulcer

About 2,000 ulcer bearing patients pass through the clinic

* Read before the Central Neuropsychiatric Association Rochester Minnesota October 6 to 8 1932

each year, of which a proportionate share is observed in the section on gastro-enterology From such a wealth of material one becomes conscious of manifestations that tend to be common to all Irregularities in gastric physiologic processes associated with ulcer can be recorded, in part at least, but not so the occult background of ulcer We are still so steeped in the traditions of the past that we look for the pathogenesis at the site of the lesion Step by step, we are shaking these inhibitory traditions from us Diabetes mellitus was considered of renal origin until in 1888 Von Mehring and Minkowski accidentally proved that it was of pancreatic origin On the other hand, physicians err by assuming almost any etiology when the truth is not known Shaking palsy was attributed to muscular changes, arteriosclerosis, thyroid disease, or merely neurosis, until Parkinson, in 1817, presented a classical description of the disease, and suggested that it might be a disease of the spinal cord that later involved the medulla

References in the literature to the neurogenic factors in ulcer are as a whole not in tune with the thought I should like to convey In 1916, Duranti, writing on the trophic element in the origin of gastric ulcer, tabulated the seventeen different general ways in which ulcer can be produced experimentally These range from interference with the nerve supply, through injury to blood vessels, infected or sterile emboli, endogenous toxins, bacteria and bacterial toxins, to local trauma and distant cutaneous burns The proponent or antagonist of any hypothesis consequently can find ample laboratory evidence to support his belief Relative to the nervous system, Duranti cited that ulcer can be produced by lesions of the central nervous system Clinically, we see this in the frequent finding of ulcer associated with tumors of the brain Duranti stated that ulcers can be produced by lesions of the gastroduodenal nerves, and he obtained most severe hemorrhagic ulcers by section, through a lumbar route, of the median splanchnic nerve and less frequently from section of the minor and major splanchnic nerves He thought that the lesions in the stomach were the result of vascular spasm stimulated by outpouring of epinephrine, actuated by nervous

influence on the suprarenal glands Ulcers produced by section of the vagus nerves were considered as the result of section of the sympathetic fibers that course with the vagus In his conclusion, Durant stated that the life of the gastric cell is dependent on the integrity of the sympathetic nervous system

With the belief that there is a psychic phase in the neurogenic etiology of ulcer, our attention has been directed away from peripheral nerves to the central nervous system In this we have the support of Cushing who postulated the presence in the diencephalon of a parasympathetic center that has to do with ulcer "From this center, apparently tuberal in situation, fiber tracts pass backward to relay with the cranial autonomic stations of the midbrain and medulla, of which the vagal nucleus is by far the most important, because of its influence on the activity of the lungs, heart, and upper alimentary tract." He gave recognition to the patient, who, suffering from nervous instability, is classified as of the parasympathetic (vagotonic) type, and who, under the stimulation of emotion or repressed emotion, is capable of developing ulcer, if extrinsic secondary causes are not wanting, such as frequent indiscretions in methods of living

The center identified by Cushing may be the region affected by a neuropathologic process, but in this paper I wish to con centrate on the psychic phases of ulcer The pathogenesis may involve inhibition of some nerves or stimulation of others, I do not know I am convinced, from clinical observation, that there is a psychic element in ulcer as it afflicts a certain type of patient These persons are part of a large class that is subjected to certain diseases, such as coronary disease, hypertension, allergic reac tions, or ulcer, and perhaps to exophthalmic goiter The patients who have ulcer are in a subgroup by themselves Their characteristics may be obscured by a calm veneer that belies the true person and that misleads the physician who is ignorant of or opposed to belief in a psychic factor in ulcer The true personality can be discovered by those who have time, patience, and understanding, and who obtain the patient's confidence Pavlov objected to applying to man his theories of conditioned reflexes in animals, yet they help the general internist to under

stand psychologic reactions in man Pavlov made his objection because reflexes in man come from a complex, confused environment that defies analysis into separate parts In his animals Pavlov could see the evidence of lack of balance between inhibitory and stimulating influences In some, excitatory processes were so strong that complete inhibition was impossible, in others, excitatory factors were so weak that the animal was inhibited beyond proper limits I think that I can see these types among patients with ulcer The difficulty lies with the inhibited type Those are the patients who make it difficult for some to accept the hypothesis that there is a neurogenic ulcer However, the inhibited person is unbalanced just as the excited person is unbalanced, and when the former is recognized, and becomes oriented, he often will overcome his fear of being classified as a neurasthenic, and with startling revelation will narrate disturbances in his environment that preceded each attack of ulcer I have found that the apparent imperturbability of farmers is frequently only external

Case I.—A farmer, aged forty-four years, came to the clinic in May, 1930, with a complaint of stomach trouble He gave a history of having had intermittent, seasonal attacks typical of ulcer for the last twenty years Roentgenologic examination gave evidence of duodenal ulcer This man had had the usual worries of a farmer, but found that when he could not get his work done his stomach troubled him for ten days to eight weeks at a time The distress was definitely worse when he was nervous or excited He also had carcinophobia in the background of his mind His fingers were the color of mahogany from smoking

When a patient's personality is of the excitatory type, he needs only orientation or elucidation to see cause and effect, thus aiding the clinician in diagnosis and treatment

Case II —A housewife, aged twenty-nine years, who had been married for eleven years, and who had two children and had experienced one miscarriage, was seen at the clinic May 23, 1932, complaining of stomach trouble of three years' duration, consisting of attacks of burning pain two hours after meals Surcease was obtained by the usual methods A small duodenal ulcer, with crater, was visualized on roentgenologic examination The patient was a vivacious Jewess, who, to quote her, was "quick on her feet" Her husband was reported to have the same type of disposition, and consequently there

was much friction in the family Her two healthy boys were a great mental strain to her She could endure eating only one meal a day with them and in order to be able to do this she had to curtail her other household duties so as to have the mental endurance to pass through the meal The patient s husband eventually became afflicted with a malignant thoracic tumor and she came to the clinic with him The thoracic tumor had been diagnosed two months previously at which time the patient had exacerbation of her symptoms Surgical interference for the ulcer was impossible because of the seriousness of the husband s condition The husband s operation was a brilliant success and the patient s symptoms disappeared In one month a second roentgenologic examination disclosed the deformity of the duodenum but the crater had entirely disappeared

Case III.—A research engineer in the gasoline industry aged thirty years came to the clinic August 17 1932 with a typical history of duodenal ulcer of thirteen years duration He had had four gastric hemorrhages the first one in 192/ Operation August 20 1932 revealed a chronic hemorrhagic duodenal ulcer

The patient was an extremely bright intellectual young man and held a responsible position He voluntarily stated that each exacerbation including the hemorrhages invariably followed a period of intensive application to the settlement of some major problem or an effort to finish an important piece of work on time. In the absence of symptoms physical exertion made no difference, but in the presence of symptoms physical exertion accentuated the distress.

Eusterman, in a chairman's address before the American Medical Association this year, gave half of his time to a consideration of the etiology of ulcer, and his dominant theme was the neurogenic influences He quoted freely from foreign authors, among whom he cited Hauser, who maintained that all of the exciting factors of ulcer are increased if the patient who has an ulcer, simultaneously manifests a neuropathic tendency Draper has emphasized the constitutional habitus rather than neurogenic factors, although he also has recognized what he calls a psychologic panel Horder expressed the belief that ulcer is made possible by the stress and strain of a complex civilization which tends to lower tissue resistance. Alvarez said that psychic stimuli of a certain type increase acidity and peptic activity of the digestive juice, with a possibility of reduction of the protective mucus Ivy once told me that he was about to abandon attempts to produce experimental chronic ulcer, because he could not get his dogs interested in the stock market. Modern en

vironmental strain has deleterious effects on all, but persons are not born with equal nervous reserve or fortitude They differ in susceptibility and response to environment

Case IV —A musician, aged thirty-nine years, lived moderately except that he used tobacco a little to excess He came to the clinic in June, 1930, with a complaint of "stomach trouble" He stated that he had always been of a nervous disposition, irritable at times, that he worried much, and took little outdoor exercise He gave a typical history of ulcer, embracing the last six or seven years He had had five or six attacks a year of dull, aching epigastric pain three to four hours after eating, with associated belching, bloating, and nausea Shortly before he came to the clinic he had had pain at night He had followed a modified diet for ulcer, with relief of symptoms, for the last two months He stated that he had never been satisfied with anything, and that since the vitaphone had come into use he had had a hard time making a living Roentgenologic examination disclosed a duodenal ulcer

Case V —A coal merchant, aged forty-three years, who used tobacco and coffee to excess, came to the clinic in May, 1930, with a chief complaint of stomach trouble He had had soreness in the median line of the upper part of the abdomen for the previous six months The soreness spread to right and to left, and occasionally appeared in the right axillary line Relief did not follow taking of food or soda He had had no actual pain Three months previously he had had tarry stools, which an osteopath said contained blood Roentgenologic examination gave evidence of a duodenal ulcer The man was high-strung His business caused him much mental strain He was president of his golf club and active in Rotary His business partner had died two years before, and he had had additional responsibilities since. He recently had consolidated the business He was very conscientious, and was afraid he might offend his physician at home by seeking medical advice elsewhere

Clinically, ulcer affects only persons of a certain stratum defined on a basis of personality The definition of this stratum is difficult, and its existence can be appreciated only by observation Its broadest limitations can be defined by considering classes beyond its bounds Because of the exceptions, the classification of people into strata, on the basis of personality, seems to fuse at the periphery, and thus the definition of a stratum is obscured Nevertheless, careful evaluation of a person's reaction to his environment will reveal information sufficient to classify him, even if irrelevant or antagonistic dominant char-

acteristics obscure those needed to group him with those among whom the ear marks of the ulcer type are self evident

Ulcer is almost entirely a disease of civilized people Ulcer is rarely encountered in the typical negro of the South, who lives under the poorest hygienic conditions this country affords, in that he has poor food, irregularly and poorly prepared, and is subjected to much focal infection because of neglect As a race negroes are considered free users of alcohol and tobacco Dr Rivers of our staff personally interviewed 200 unselected negroes in Texas, and only once did he obtain a history suggesting ulcer Sixty women and 140 men were interviewed One man gave an inadequate but suggestive history of ulcer This negro's wife commented on his unusual nervousness I have had four negro patients with ulcer, two were physicians, one was a realtor in Chicago, and one a train porter on a short run, who also had to act as Pullman conductor, a position of responsibility which might easily have resulted in strain for one of his grade of intelligence

I have spent some time in Latin America While in Mexico for two months, a year ago, I endeavored to elicit a history of ulcer among the Indians, but failed Dr Montaño, of the Department of Health in Mexico, verified this observation when he recently told me that the idea was prevalent among Mexican physicians that the Indian rarely has ulcer His colleagues collected records from an out patient service of 400 patients with histories like those obtained in cases of ulcer, but not in one were they able to demonstrate an ulcer roentgenologically He said that if they missed a few the incidence still was low I can conceive of no lower standard of living adopted by anyone who is in contact with civilization than that of the Mexican Indian He has nothing, just that, nothing but the most inadequate of foods, highly seasoned, and tobacco and alcoholic excesses are part of his life He lives in filth, dirt, ignorance and poverty He accepts, as a whole, no medical care, certainly no prophylactic care He has nothing, he knows nothing, and praises be, he wants nothing He is contented, absolutely contented, with his lot in life divorced from the complexities,

worries, anxieties, fears, and apprehensions of higher civilization, and he inherits from his Aztec ancestors a stoic philosophy and a nervous system with excitatory and inhibitory factors well balanced Mind you, I am not talking about the Spaniards but the true Mexican of Aztec descent The citizen of Mexico, of advanced standards of civilization, is as likely to have ulcer as anyone

Case VI —A cashier of a bank in Mexico, aged forty-five years, who used tobacco to excess, came to the clinic in March, 1930, with a complaint of "stomach trouble and nerves" He had had hyperacidity for ten years, with occasional attacks of epigastric pain lasting thirty minutes, which radiated to the right side of the thorax posteriorly Apparently the pain was moderately severe It was relieved by taking of soda The patient was very nervous, impatient, and high-strung He had worked in a bank since he was twelve years of age, had passed through the financial turmoil of Mexico, and several times had been taken from his home at midnight by bandits who had made him open a vault, and so forth He walked the floor at night, and smoked cigarettes incessantly, but had felt well, and had been free of symptoms after his arrival at the clinic Roentgenologic examination gave evidence of a duodenal ulcer

Medical missionaries tell us that the Chinese coolie does not have ulcers It is true that this may be the result of a racial or geographic distribution The incidence of ulcer on the continent of Europe is reported to be lower than ours, but I feel that the deciding factor is the difference in the nervous status, in the personality of the individual, and in his nervous response to his environment

When ulcer is encountered among persons who are not of the highly civilized, intellectual stratum of society, careful consideration of the patient's reaction to his environment often will disclose a hidden condition of strain, at first unsuspected, but nevertheless present, that affects his nervous system so that ulcer is possible It may be hard to recognize this condition of strain The outward manifestations of his reactions may be blanketed, perhaps not voluntarily so, but naturally, that is, he is like the inhibited type of animal of which Pavlov wrote Bollman tells me that dogs stimulated by the presence of a cat may manifest outward signs of excitement and at the same time

have an elevated blood pressure, whereas other dogs similarly stimulated may show no outward signs of excitement, but their blood pressures are nevertheless elevated There is no abstract method of measuring a patient's response to his infinitely complex environment, but the quiet person who reacts to a stimulating environment so as to change his nervous functions in a certain way can be classified as a patient susceptible to ulcer

The other extreme is the highly sensitive, intellectual patient who is capable of analyzing himself He can, with help, give information that shows the direct influence of nervous reactions on the origin and exacerbation of the syndrome of ulcer Often this information is volunteered by the patient

Case VII.—A salesman aged forty three years who used tobacco excessively and some alcohol first came to the clinic in January 1929 with a history of clear-cut, recurring epigastric distress of fourteen years duration. He was high strung and nervous. Operation January 11 1929, revealed a subacute duodenal ulcer with duodenitis also diverticulum of the duodenum and chronic appendicitis. Operation consisted of knife excision of the ulcer closing as a gastroduodenostomy excision of the diverticulum and appendectomy The patient returned in November 1929 with recurrence of his distress, and in spite of the operative interference for the cure of ulcer he had the hyperacidity and roentgen deformity characteristic of recurring ulcer of the duodenum In a letter dated August 23 1932 he wrote, My well known duodenum is still quite a disturbing element in my anatomy Each night I set the faithful glass of milk by the bed and occasionally take a bromide or something stronger Of course it is simply a case of fractious nerves I try to control them, but it seems that they are a bit too strong for me. In short it seems to me that if I do not get control I will need to return for another operation I believe that a six months vacation might be effective. I happen to know that this man has an unruly daughter to whom he is devoted and for whom he endures much

The stimulus to exacerbation of ulcer may be a sudden shock.

Case VIII.—A physician aged fifty two years, had undergone posterior gastro-enterostomy in 1915 for uncomplicated duodenal ulcer He came to the clinic September 5 1932 He had had perfect health following the operation in 1915 until June 1932 when he struck a man with his automobile and killed him The nervous strain on this nervous physician who was a victim of migraine, pylorospasm and possibly ulcer accentuated his symptoms and a month later he had a primary hemorrhage Roentgenologic

examination gave evidence of deformity of the duodenal cap, probably due to ulcer The gastro enteric stoma was free At operation, September 22, the only abnormality found was a duodenal ulcer

The exciting cause may also be a slow, continuous process

Case IX.—A nurse, aged fifty-two years, a widow with one child, under went operation at the clinic in July, 1920, for a perforating duodenal ulcer Posterior gastro-enterostomy was performed Appendectomy was done, also, for chronic appendicitis In the spring of 1932, the patient suddenly had a gastro-intestinal hemorrhage Subsequent roentgenologic examination re vealed a duodenal ulcer The historical evidence, other than hemorrhage, was minimal She said that she was certain that a mild period of symptoms typical of ulcer had culminated in a hemorrhage, implying an extension of the ulcer These symptoms she attributed to extreme financial worries, so acute that she did not know how she would provide food for herself and son The career of her son is known to be a constant source of worry The pa tient's response to medical treatment was satisfactory until she recently lost her position, then there was exacerbation of her pain, but no further bleeding

When one learns to recognize the type of ulcer-bearing patient, one can predict that an ulcer is present almost without other aids, at least the diagnosis can be as accurate as could be made by Moynihan, who once said that he could diagnose an ulcer by correspondence This knowledge on the part of the physician approximates in importance the typical history of ulcer in arriving at a diagnosis To describe the type so that others can recognize it is difficult The term "nervous exhaustion" is used, but when applied to patients with ulcer it does not imply an apathetic person, with imaginary or multiple functional symptoms It implies a man who is encountering obstacles that prove to him a trial and handicap, which he must, because of his nature, endeavor to overcome

Case X.—A saleswoman, aged thirty-nine years, single, came to the clinic in June, 1930, with a complaint of stomach trouble, which had begun ten years before, when she was having very severe sick headaches each Saturday night She and her sisters ran an exclusive ready-to wear shop for ladies She was working very hard, day and night, doing the buying in New York City, and selling the goods to the public. She had attacks of hyperemia in the left hand and arm, and also began to have typical symptoms of ulcer She went on a vacation and changed her habits of living, and all of her trouble

disappeared except for an occasional day or two of distress At the time of the crash in the stock market her symptoms returned for the crash affected her business and also at no time could she allow her women customers to know that she was anything but successful and free from annoyances She always had to put her best foot forward Roentgenologic examination gave evidence of duodenal ulcer

Case XL.—A captain in the Salvation Army aged forty seven years came to the clinic August 1930 with a chief complaint of recurrent attacks of tonsillitis during the last eight to ten years. He also complained of distress typical of ulcer In his youth he had heartburn and was told that he had ulcer In recent years he had had distress in the autumn and winter This distress always related to the acute activity of his work during this season He approached autumn with apprehension because of the many poor people to look after After the holidays the distress lessened Roentgenologic examination gave evidence of a duodenal ulcer

A calm exterior may obscure a turmoil, an inward nervousness that may, and probably does, produce greater somatic reactions than those of the individual who has no pent up emotions Persons so situated in life are prone to ulcer Divorce them from their environment and symptoms of ulcer often disappear How many times have we been told by patients, "Why, Doctor, when I was at work at home I was having a terrible time with my stomach (meaning ulcer), and when I got on the train to come to Rochester I said, I'll eat anything, and, do you know, Doctor, I have never had any trouble since leaving" Then comes the old bromide, "It is like going to the dentist with a toothache" Many an executive, against his judgment has been induced by his friends to go hunting in Canada, his judgment, in turn, having become distorted by attention to his duties, so that he thought he could not leave his business, besides, he had stomach trouble Yet, in the woods of Canada, he ate camp food, smoked, drank liquor, slept little, and did hard physical work, to which as an office worker, he was not accustomed, but he had no distress typical of ulcer Such a man has left the exciting factors of his environment behind, and the ulcer becomes quiescent The nonsurgical treatment of an ulcer is most efficacious if conducted with the patient away from his home town he cannot answer the phone, well meaning friends

cannot keep him stimulated by frequent calls to his sick room He is worse off if treatment is tried in his home rather than in a hospital Sedatives do much, when they work efficiently, in affecting the healing of an ulcer Bromides were formerly our favorites, but now we select one of the derivatives of barbituric acid These drugs are of greatest help when the patient will not let go, when he lies in bed fairly on top of the tufts of the mattress rather than relaxing

In a disjointed way, I have tried to picture a personality that we can recognize as of the ulcer type Knowing this type, we can anticipate the presence of an ulcer, and can predict concerning patients who will have recurrences after medical cures, and gastrojejunal ulcers after surgery There is an impression gained from mannerisms and gleaned from narration of minor details that makes the type characteristic I do not know the mechanism by which it works The personality of the patient is the inciter to the ulcer and its exacerbations It is the soil on which the seeds of ulcer mature, the seeds being the commonly accepted causes Unless the seeds fall on fertile soil, ulcer does not result, furthermore the soil may be waiting, but, unless the seeds are there, chronic ulceration does not result Lack of these two conditions, together, is why many persons with unbalance of the nervous system do not have ulcer Failing in this, they may become patients with hypertension or coronary disease

Case XII.—A traveling salesman, aged fifty-one years, who previously had used tobacco to excess, first came to the clinic in June, 1915, when a diagnosis of duodenal ulcer was made He had had symptoms of ulcer in 1905 He returned to the clinic in June, 1932, because of the development of glycosuria and substernal pain His attacks of ulcer had occurred frequently until the autumn of 1931, when anginal symptoms developed, the pain of which stopped his activities According to the man's own words, "I have been a hard-working fool, working eighteen hours a day and sleeping four" When his anginal pain developed he could not be active, physically or mentally, and his symptoms of ulcer immediately became quiescent, he had resigned himself to his fate. A letter from his physician at home, dated July 6, 1932, gave the information that the patient had suffered a very severe attack of angina that morning and had died A postmortem examination was not made

Acute ulcers may appear, independent of secondary causes, even producing hemorrhage if the acute ulceration or inflammatory-like process involves a blood vessel, but the true, chronic, calloused ulcer requires all factors to produce the lesion that one can often palpate through the wall of the viscus when the abdomen is open

A CLINIC ON ACUTE, OLD-FASHIONED GOUT, WITH SPECIAL REFERENCE TO ITS INCITING FACTORS

PHILIP S HENCH AND CHARLES M DARNALL

"Acute old fashioned gout is an almost extinct disease," according to a recent editorial [7] This attitude has been repeatedly expressed since the World War and the advent of Prohibition, and the subject of gout seems recently to have been neglected if medical literature is an index of interest therein For the last fifteen years there have appeared in all journals printed in English a yearly average of only two articles on this disease Contributions in other languages have been only a little more numerous We, who see an average of about two cases of gout each week, cannot subscribe to the viewpoint suggested in this editorial, and cannot relegate "acute, old fashioned gout" to the category of extinct diseases

The manifestations of gout in joints, such as the "podogra" or painful great toe, and gouty arthritis elsewhere, are the commonest features of the disease So outstanding are they that gout is often defined as an inflammation of the joints In this sense gouty arthritis equals gout There is, of course, more to the disease than this, and the manifestations in the joints are not the disease in toto, but merely its dominant symptom Seeing the disease whole, the three major somatic expressions of gout are (1) Acute, later chronic, arthritis, (2) tophaceous deposits, and (3) abarticular or visceral gout, characterized by late or terminal specific changes in organs, chiefly, perhaps exclusively, in the kidneys Associated with these features, sooner or later, there is hyperuricemia, of variable degree and permanency which is the humoral expression of gout

Aside from the appearance of tophi, there are two stages to the disease The first stage expresses itself as an acute, recurrent

form of arthritis with complete remissions, generally associated with transient, sometimes with permanent, hyperuricemia The second stage is one of chronic arthritis generally with persistent hyperuricemia, and with or without clinically demonstrable visceral lesions, such as specific lesions of the kidney and the generally nonspecific lesions of associated cardiovascular disease Tophi may make their appearance in either stage but do so much more often in the second

Uratic tophi are the only known specific lesions of gout, and the diagnosis of proved gout rests on the discovery of their presence Before their appearance a diagnosis of presumptive gout is justifiably based on the presence of several of the other phenomena mentioned Thus, the diagnosis of gout falls into two categories, that of (1) presumptive gout, or "pretophaceous" gout, and (2) proved or tophaceous gout

Returning to the subject of acute, old-fashioned gout Although many of our patients when we see them have gout in its chronic articular form, practically without exception they have passed through the classically characteristic phase of acute recurring bouts followed by complete remissions, the "chain of fits" as Sydenham called it

An inciting cause of gout is one which is followed more or less promptly by an acute paroxysm of arthritis Such a cause is contrasted with a predisposing cause, which merely confers a tendency to the disease Little is definitely known of these predisposing causes although they are believed to be linked with factors of heredity, sex, age, habitual excesses in food and drink, and chronic exposure to lead

The story of gout through the centuries has revealed the inciting causes as consisting of a number of quite different factors, which are able, although not infallibly, to provoke attacks with variable promptness and of variable severity The determinants of an attack of gout are generally listed as dietary errors, major physical trauma such as fractures and dislocations, minor physical trauma, trivial shocks such as are provided by vaccination or extraction of teeth, physiologic trauma such as results from protein therapy, severe purging, loss of blood

through venesection or other means, exposure to cold or wet, sexual excesses, and the nervous trauma of acute worry, sudden mental strain or violent outbursts of passion By errors of diet are here meant episodal rather than habitual indiscretions, the sporadic ingestion of foods in unusual amounts Varieties of minor trauma may be the precursors of a paroxysm, a new or tight shoe, or the unaccustomed exercise of a golfer's holiday on which extra holes are played, of a city dweller's vacation hike, of a desk worker's amateur excursions into manual labor We heard one complaint that gout followed long standing on a ladder while painting the garage. These events are not invariable provokers of an attack, and their potency in inducing acute reactions perhaps depends, as Garrod expressed it, "on the proneness of the patient's system "

We present here five cases of gout seen at The Mayo Clinic during the month coincident with the appearance of the editorial mentioned

REPORTS OF CASES

Case I.—A prosperous miller aged seventy years, came to the clinic complaining of pain redness and swelling of the left great toe. The symptoms had appeared acutely four weeks before. Until the man was fifty years of age he had had no trouble with joints Then he had begun to have occasional dull soreness in the metatarsophalangeal joints of either great toe lasting at the most two or three days and associated with a little redness for a few hours only There was no swelling and he thought the attacks were due to bunions. These brief periods of pain recurred at infrequent intervals and generally followed unusual exercise, such as a walk of unaccustomed length or dancing The patient had done considerable dancing while on his honey moon at the age of fifty three years. A Greek restaurant keeper had given him gratuitous advice on several occasions 'You have gout. It will go away but some day it will come back again

September 23 is the patient s birthday habitually celebrated by a Dutch lunch Following this celebration in 1928 he had experienced gradual onset of pain and soreness in the metatarsophalangeal joint of the great toe. Increasing gradually the pain became excessive a few nights later By morning the toe was markedly swollen and beefy red. So intense was the pain that the weight of the bedclothes or jarring of the bed was agonizing He had been treated by hot applications and capsules and had made a slow but complete recovery in about twelve weeks. The skin of the affected regions peeled off in large pieces as the process subsided A diagnosis of infectious arthritis had been made and two infected teeth had been extracted in the course of his convalescence. Since this first

frankly acute attack, he had noted continuation of brief episodes of soreness in one or the other great toe, lasting from two to three days, with no redness or swelling, and again induced by minor trauma or exercise In the autumn of 1928 he also had experienced, while walking, sudden dyspnea, with sharp substernal pain and a sense of constriction of a few minutes' duration This had recurred occasionally on exertion and a diagnosis of angina pectoris had been made.

The man had not felt very well at the time of his last birthday, and had postponed his "Dutch lunch" until April, 1932 He prides himself on being a connoisseur of food, and he attempted to excel all previous feasts on the occasion mentioned The menu included tomato juice, two kinds of caviar, sardines, goose liver, corned beef and cabbage, sauerkraut, Limburger, Swiss, and many other varieties of imported cheese, mackerel in white wine sauce, smoked, plain and spiced pickled herring, rye bread, tomatoes and potato chips His custom was to provide at each feast some exotic dish, and the piece de résistance on this occasion was mammoth meat imported from Siberia This was reported to have been frozen in the ice of Siberia for thousands of years, and thus kept in a state of perfect refrigeration Previously mined only for the Russian Czar, it is now smoked, dried, and imported in limited amounts at fancy prices, and advertised as ready to eat The patient, however, had boiled the meat "to prevent death by some prehistoric germs"

"It may have been mammoth meat or dog meat," he said "So far as I was concerned it was mammoth meat and the party accepted it gleefully as such, licking the platter clean"

The liquid refreshments were equally varied and numerous There was near-beer fortified with grain alcohol, gin, a little left-over prewar whiskey, dry martinis, manhattan cocktails, crème de-menthe, with homemade grape wine recurrently Along about midnight he made a mixture of all of them, which concoction was unanimously voted the most palatable of all

The next day nothing happened to the patient's joints, but during the week he tried to get rid of the alcoholic remnants At the end of a week, in the night, his left great toe became acutely painful, red, and swollen The patient consulted a physician who had not seen him before, and a diagnosis of infectious arthritis was again made However, a search for foci of infection gave negative results Pills and hot packs were provided, but gave no relief The man was confined to bed four days, and had been walking with difficulty between that time and his admission to the clinic in May, 1932

The patient's ordinary dietary habits include one generous serving of meat twice a day, liver once a week, occasionally brains, anchovies frequently, whiskey two or three times a month, and two quarts of wine each month Members of his family, so far as is known, have not had gout, rheumatism, or other trouble with the joints The patient's past history was essentially negative

Arcus senilis, graded 2, was present Also, there were two devitalized teeth, small, fibrous tonsils and arteriosclerosis of the peripheral vessels, graded 2, but no cardiac enlargement The joints were negative to examination, except those of the left foot This extremity was swollen and red

up to the ankle, and there was tenderness graded 3 of the metatarsophalangeal joint of the great toe the tenderness was most marked over the mesial aspect of this joint. No tophi were present The temperature and the pulse rate were normal. Blood pressures were 150 mm of mercury systolic 90 diastolic Roentgenologic examination gave evidence of bursal thickening over the first metatarsophalangeal joint of the left great toe. The values for certain constituents in each 100 c c. of blood were as follows uric acid 6 7 mg (normal 3 to 5 mg)* urea 32 mg sulphates, 5 4 mg The urine was negative to examination and the water concentration test and water dilution test gave results that were normal The electrocardiogram gave evidence of sinus arrhythmia left ventricular preponderance, and delayed auriculoventricular conduction time. The P R interval was 0 24 second and the QRS complex was slurred in all leads.

A diagnosis of presumptive gout acute, recurrent gouty arthritis and angina pectoris with coronary sclerosis was made Wine of colchicum and a diet free of purine was prescribed Hot packs were applied to the affected part After three days although the value for blood uric acid was still ele vated (6 9 mg in each 100 c.c.) the swelling had markedly subsided and the tenderness was reduced so that the weight of the body was well borne Skin of the great toe was being desquamated The man was then given cinchophen 7 5 grains (0.5 gm) three times a day for three days, in addition to the purine-free diet When dismissed he was walking well with only slight pain on deep pressure over the affected joint. For the cardiac condition theobromine and sodium bicarbonate, each 5 grains (0.3 gm.) three times a day were prescribed in addition to restriction of activity

As an example of a magnificent indiscretion for a person with gout, this patient achieved a triumph which could hardly be surpassed He felt that his attacks were related to different types of incitants, minor physical trauma, as well as gastronomic sprees The general experience of patients with gout in modern times demonstrates that, as of old, these agents should still be considered potent excitors The teaching has been that a gastronomic debauch is a greater menace to those subject to gout than an injury, and the teaching seems to be justified in this case, the attacks which this patient had after his feasts were much more severe and of much longer duration than those brought on by trauma However, trauma induced exacerbations more promptly than dietary excess Whereas an attack seemed to follow a slight injury by a few hours, or at most a day, several

* Folin Otto An improved method for the determination of uric acid in blood Jour Biol. Chem 86 179-187 (March) 1930

days of perhaps ominous calm preceded the more violent explosions which resulted from, or at least followed, major dietary indiscretions

The association of gout and angina pectoris is not uncommon Yet it is doubtful if the pathologic changes inducing angina pectoris in such cases are truly those of gout The only recognizable specific lesion of gout is the tophus, or precipitate of urate in tissue, and examinations of cardiac and vascular tissues, in cases such as this rarely disclose these deposits A true "gouty heart" in the sense of intracardiac tophi, rarely exists A few presumably authentic cases have been described [3, 5, 13, 16, 21] One of us (Hench) saw in Munich the heart of a patient of von Muller and Brogsitter in which complete heart block was found to be caused by a large and clinically proved urate tophus affecting the conduction bundle Practically all authors, from Garrod[15] (1859) to Gudzent (1928) have agreed that true gouty endocarditis is very rare, and gouty myocarditis practically nonexistent Atheromatous changes in the heart and blood vessels of patients with gout do, however, occur frequently, and Gudzent has expressed the belief that many patients who die of "gouty heart," in reality die of cardiac hypertrophy with fatty degeneration Senator called these cardiovascular changes not gout itself but complications of gout In the absence of deposits of urate they do not represent true visceral gout and cannot be considered the analogues of articular deposits

The writings of Osler, Gudzent, and Gemmel have led physicians to expect hypertension in association with gout, but in this case and the subsequent cases noted in this paper, the blood pressure was not particularly elevated Allbutt's expressed belief was that regular gout and high blood pressure are not more than incidentally associated During the acute paroxysm the blood pressure may be elevated, but the pressures of young persons who have gout may be normal and remain so in spite of activity in the joint for many years Von Muller and Fishberg found high blood pressure uncommon in gout Rosenbloom, studying four cases of gout repeatedly over a period of ten years, found that between attacks the blood pressure tended to be below rather

than above normal, but an elevated blood pressure was present during an acute attack.

Case II.—A Jewish salesman twenty-seven years of age, entered the clinic May 19 1932. Four weeks previously he had been awakened about 5 a.m. by exquisite pain in the left great toe followed at once by swelling and a local sensation of heat. He had never before had any trouble with his joints. During the first day and night the pain subsided a little, to recur acutely in the early hours of the third day. There was no fever and no other joints became involved. A diagnosis of gout was made by his physician and he was told to eat no meat except liver and chicken. Heat and rest were advised and he remained in bed for two weeks. He then attempted to get about but the pain was aggravated and he again kept off his feet. He came to the clinic because his condition did not improve.

The patient's past medical history was negative except that an acute perinephritic abscess had been drained at the clinic in 1923. The family history was negative for gout or other disease of the joints.

Obesity was graded 2. The patient's height was 5 feet 7 inches (170 cm.) and his weight 184 pounds (83.5 kg.). The genitalia were atrophic as a sequel of mumps. The left great toe was swollen graded 2 and was very red and tender. Swelling extended to the ankle. Maximal tenderness was rather markedly localized to the mesial aspect of the great toe at the metatarsophalangeal joint. No tophi were found. The roentgenogram of the left foot gave no evidence of abnormality. The value for uric acid was 6.2 mg. in each 100 c.c. of blood. Examination of the urine was negative. The blood pressure was 120 mm. of mercury systolic and 70 diastolic. Temperature and pulse were normal.

We confirmed the diagnosis of presumptive gout. On first questioning the patient could not recall any circumstances which might have precipitated this, his first attack. When asked about his recent habits regarding food and drink he recalled that the attack had come on the fourth day of his participation in April in the feast of the Passover when he had indulged freely and unusually in wine, chicken and meats. Ordinarily he used alcohol only about three times a month; he ate heartily of meat although not of the meats in which there is high concentration of purine, liver, sweetbreads and so forth.

Treatment was outlined to be used at home, for the patient could not remain at the clinic. Three weeks later his physician found the value for uric acid to be 4.2 mg. in each 100 c.c. of blood and in a subsequent letter the patient informed us that acute exacerbations had entirely disappeared.

The association of the feast of the Passover and this patient's initial attack of gouty arthritis will be considered later. It will be recalled that the patient had been advised to eat no meat but liver and chicken. Of these, liver, which is particularly rich in purines, is generally one of the foods most rigidly prohibited in

gout Although this patient rarely had eaten liver before, he had followed advice, and was eating it in rather generous quantities This may or may not explain his lack of improvement in spite of rest and application of heat Also, it may explain the prolongation of his attack prior to his admission at the clinic, and the high value for blood uric acid in his initial attack It is not our usual experience to find such definite hyperuricemia in the first, or even in the earlier subsequent attacks

Some physicians believe that patients with gout practically[4, 9, 10, 14, 27, 28, 34] always have permanent hyperuricemia, and that it increases especially during an acute bout Others report that the uric acid content of the blood is decreased during an attack On the contrary patients have been noted whose blood urates have been moderately increased or of normal concentration between attacks, who demonstrated, during an attack, neither a rise nor a fall from previous values It seems strange that there should be such disagreement, in view of the extensive work done on the purine metabolism in gout Three things are responsible, true fluctuations of blood urates in the same or different individuals in the same stage of different attacks, differences in methods used for the determination of uric acid, and lack of enough repeated blood estimations on the same patient in different stages of the disease

Case III.—A Jew, aged forty-seven years, presented himself at the clinic, May 20, 1932, the day following admission of the patient in Case II He was suffering with severe swelling, redness, and pain of the right great toe, of four weeks' duration He volunteered the information that it had come on acutely in the morning of the third day of the feast of the Passover at which time he had indulged in unaccustomed degree in meats and wines He had been wearing a new pair of shoes for the occasion, but had discarded them on the second day of the feast, for both feet seemed hot and uncomfortable The following day the right foot was acutely swollen and painful His physician had raised the question of thrombo-angiitis obliterans (Buerger's disease) Hot applications and rest gave some relief, but the pain persisted, and he had tried applications of cow manure with, as he said, some benefit

Seventeen months previously he had had a sudden attack of acute arthritis of the right great toe. He had had influenza and had taken a few ounces of whiskey as a tonic on three successive days About two days later the acute arthritis appeared The attack lasted for five days and subsided completely no diagnosis was made His habits as to drinking were very

irregular although he drank perhaps, a gallon of whiskey in six months. He ate meat once a day, but heavily then Frequently he indulged in a half pound of liver but enjoyed none of the other foods in which there is high concentration of purines. His past medical history was negative and there was no known history of gout or of disease of the joints in the family

On examination at the clinic the man presented typical signs of acute gout The great toe was red swollen to grade 3 shiny and still exquisitely tender The tenderness extended over the entire great toe but centered at the mesial aspect of the metatarsophalangeal joint The swelling extended over the dorsum of the foot which was cyanotic. The vessels of the extremities were patent and no pain of claudication could be elicited No focal infection was found and physical examination otherwise was negative except for obesity graded 2 His height was 5 feet 7 inches (170 cm) and his weight 188 pounds (85.3 kg) No tophi were present The blood pressure was 128 mm of mercury systolic and 94 diastolic. Temperature and pulse rate were normal A roentgenogram of the right foot gave evidence of periarticular swelling only The value for uric acid was 5 mg in each 100 c.c. of blood and for urea on the same basis 32 mg The Wassermann reaction of the blood was negative and analysis of the urine gave negative results

A diagnosis of presumptive gout was made On a purine free diet together with wine of colchicum the toe began to improve immediately and the value for uric acid four days later was 4 2 mg in each 100 c.c. of blood Cinchophen was then given and the following day the toe was almost normal in appearance. On the eighth day of treatment the patient was seen walking the hall with each step stamping his foot vigorously and without pain as he said to toughen it up The value for uric acid was then 4 1 mg in each 100 c.c. of blood and the patient was dismissed to continue treatment at home. Nine weeks later he wrote that he had been working regularly walking without pain and feeling well

A new or tight pair of shoes is often considered by the patient as the inciting cause of an attack of gout Such trauma may well be responsible Sometimes, however, we suspect that the tightness may be due not so much to the shoe, as to premonitory swelling of the foot prior to the acute onset of symptoms Patients with gout should be advised, however, to have new shoes fitted with particular care to avoid unnecessary trauma to the feet

The part played by dietary indiscretions in precipitating exacerbations of gout seems well demonstrated in Cases I, II and III

A review of the details of the feast of the Passover (Cases II and III) will indicate how it might readily provoke a paroxysm of gout This ritual is performed once a year, generally about April, and it lasts for eight days On the first two nights is held

the Seder, a ceremonial feast The first part of the four-hour ceremony involves reading of the Haggadah, or narrative of the Passover, prayer, and songs At four stated periods the drinking of a glass of wine is required as a token of festivity By some it is merely sipped, others consume the four cupfuls, perhaps 16 ounces (about 500 c c) in all Mead, apple cider, or any fruit juice, or raisin wine is commonly used Some provide wine of home manufacture, although many obtain a special Palestinian grape-wine The only difference of the latter from ordinary grape-wine is that it is fermented in Palestine in kegs reserved especially for such purposes This first part of the Seder is followed usually by a very elaborate dinner of richly cooked and highly seasoned foods in great abundance An orthodox menu is somewhat as follows Dumplings in soup, "gefullte fisch", hard cooked eggs, crackers with horse-radish (the "moror" or bitter herb symbolic of the bitter experiences of the people), fowl of some sort, generally chicken, onions, watercress or parsley, sometimes noodle pudding, the "haroses" or mixed vegetables, and a dessert Haroses is a mixture of apples, blanched almonds, and raisins finely chopped, flavored with cinnamon and wine Gefullte fisch is prepared by separating the fish skin, removing the meat, chopping it up with a mixture of onions, celery and peppers and refilling the skin and boiling Carp, whitefish, and pike are generally used All foods are richly seasoned and include considerable fat Whiskey is not used and no further wine is taken generally On the remaining six days of the Passover, menus are not dictated by custom except that no leavened bread is permitted Matzoh, the unleavened bread of affliction, made of flour of wheat, barley, spelt, oats or rye, is eaten Meat or fowl, especially chicken, is generally consumed in unaccustomed quantities Wine is not required but is often served

Wine and other fermented beverages supposedly contain no purine, yet they are known to disturb an otherwise apparently "balanced" purine metabolism Their alcoholic content is supposed to interfere in some way with the adequate functioning of whatever organs are chiefly responsible for handling purines If it is the alcoholic content of these beverages that is responsible

for attacks of gout, distilled liquors, which contain a far higher percentage of alcohol than wine or beer, should be more harmful Yet it has long been considered that fermented liquors are more likely to cause gout than distilled spirits Recently Widal advanced the hypothesis that gout is an allergic disease, and that particular wines are aggravating to certain people because of the yeast proteins they contain, an hypothesis approved by Llewellyn

The recent work of McDonald and Levine indicates that certain wines, beers, and other fermented beverages do contain appreciable amounts of purine from which uric acid can be obtained through the synthetic action of microörganisms present therein. To them it seems probable that it is the purine and not the alcoholic content that constitutes an important predisposing cause of gout

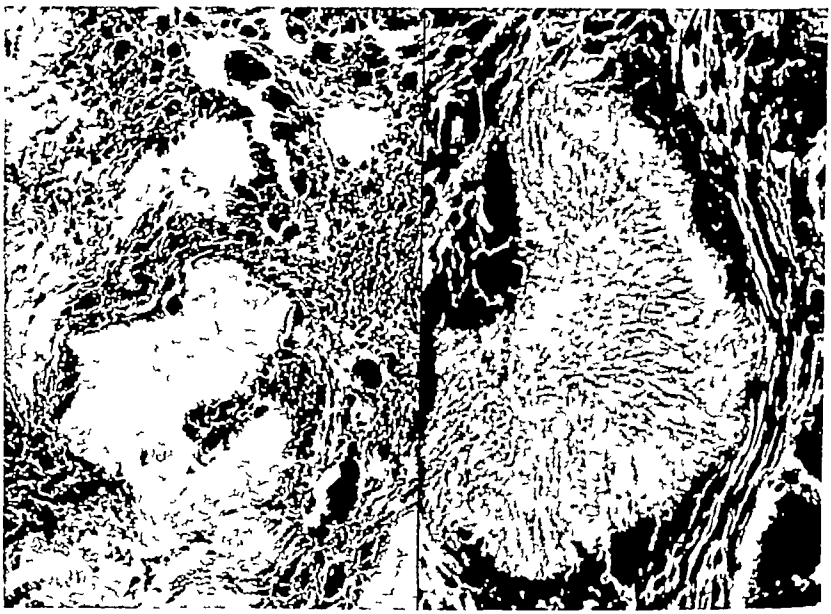
The purine content of the Passover feasts can only be guessed at Suffice to say, the menu here outlined breaks most of the dietary rules considered necessary in gout Is it not possible that the feast of the Passover is responsible for a special, if minor, epidemic of acute gout among Jews in the spring?

Case IV —We were asked to see a Jewish patient aged sixty two years in an attack of acute arthritis of the knees and left great toe which had come on while he was in the hospital on the fourth day after the first stage of a Mikulicz operation for advanced carcinoma of the colon. Asked about his trouble he told us he had had infectious arthritis over a period of twenty years. On inquiry it was found that he had had many acute attacks of arthritis in the first thirteen years each followed by complete remission. The first attack which came on the day after an alcoholic debauch involved the right great toe only The pain attained its maximum in about two weeks, and then gradually receded He was in a hospital for four weeks and it was seven weeks before the condition subsided completely Subsequent attacks, often beginning in the great toes, occurred usually in the autumn and spring and involved many joints including the knees, hands and elbows Each lasted for from three days to six weeks and then disappeared completely full function of the affected joint being restored There was no fever during attacks

After thirteen years the clinical picture had begun to change and for the last seven years the arthritis had been chronic, with from twenty to thirty minor acute exacerbations, none followed by complete remissions. One physician had made a diagnosis of gout and had tried remedies for gout for a short time. However for years since then the patient had been treated by several physicians for chronic infectious arthritis.

Lumps had appeared under the skin of the elbows and ankles in the last six or seven years There was no history of renal colic or other renal involvement The patient's habits included eating of large helpings of meat twice a day, and two or three drinks of Scotch whiskey a day His past medical history included syphilis at the age of twenty-one years, and considerable antisyphilitic treatment for the last four years No member of the family, so far as known, had been troubled with gout

The left great toe was red and tender The knees were moderately distended with fluid, and were painful and tender The olecranon bursæ were markedly enlarged, thickened, and contained tophaceous masses Smaller



A B

Fig 218 —Case IV A, Gouty tophus showing deposits of urates and surrounding fibrocytes, lymphocytes, and giant cells B, Clefts probably represent former sites of crystals (high power)

tophi were present about the left great toe and dorsum of the foot One was excised, and consisted of crystals of sodium urate, of which a murexide test was positive A foreign body giant cell reaction was present (Fig 218) Physical examination, otherwise, gave essentially negative results

The roentgenogram of the foot contained the characteristic punched out areas of gout, that of the elbows gave no evidence of bony change, that of the knees indicated that there were some hypertrophic changes The value for uric acid was 6 5 mg in each 100 c c of blood, and that for blood urea, 26 mg on the same basis The results of the Kahn and of the Kline test were 4 plus

In the four months that the patient was under observation in hospital

there were six exacerbations of gouty arthritis The first acute exacerbation occurred on the fourth day after the first stage of the Mikulicz operation the second on the fourth day after the second stage of the Mikulicz operation, which was also the first day after the first application of two clamps the third, on the first day after the second application of one clamp and the fifth on the fourth day after closure of the colonic stoma The fourth exacerbation occurred early on the day following injection of a new endocrine preparation Whether this was in any way responsible is problematical In the afternoon several hours after onset of the exacerbation one clamp was applied and this was the only surgical procedure experienced by the patient which was unattended by an exacerbation beginning soon thereafter possibly because an exacerbation was already in progress During all this period the diet was purine-free, cinchophen was not given and the value for uric acid was falling from 6 5 mg to 4 9 mg in each 100 c.c. of blood A week before closure of the colonic stoma the concentration of blood uric acid for each 100 c.c. was successively 4 6, 5.3 and 4 9 mg Two days after the closure the value had risen to 7 1 mg which might have led us to anticipate the exacerbation on the fourth day The sixth exacerbation occurred on the second day after a change from a purine free diet to a diet fairly high in protein this change was made to test the patient s tolerance.

The number of days between the various exacerbations was so different (eleven, five, seven, eight, forty seven, and seven teen days, respectively) that there seemed no regular periodicity to account for them If, then, four of the acute exacerbations suffered by this patient actually were, as seems likely, related to various surgical experiences, it is interesting to note that the major insults, the first and second stage of the Mikulicz operation, and later the closure of the colonic stoma, were not followed by an exacerbation until four days had elapsed, while the minor surgical trauma incident to application of a clamp seemed to be followed by a more prompt reaction in the joint, appearing after one day only In Case I, also, the reaction following major insults such as gross dietary errors seemed to have been delayed whereas the minor insults, such as slight trauma, were followed by quicker response Further observation on the speed of action of and the type of reactions induced, by different determinants, with the same patient, would be of interest It would seem that some inciting agents provide the basis for a prompt response, whereas others furnish a type of insult which, if eventually more potent, must overcome a latent period before their malevolence receives expression

Case V —We were called to see a Jewish woman, aged fifty-three years, on account of the sudden occurrence of acute arthritis the day following dilatation and curettage of the uterine cervix, with removal of a polyp by cautery

At the age of twelve years she had had scarlet fever with acute inflammatory rheumatism, the latter causing pains in the joints, necessitating rest in bed for three months Then function of the joints was completely restored, and no cardiac involvement ever had been apparent She experienced no further trouble with her joints until she had become obese five years before we saw her since which time she has had had occasional twinges of pain in the knees Besides the attack following the operation on the uterine cervix, three short attacks of severe, acute pain, followed by complete remission, had occurred previously one in April, 1929, which affected both knees for two weeks, one in August, 1930, which affected the right wrist for four days, and one in April, 1931, in which the right great toe was involved in a

Fig 219 —Case V Mesial aspect of joint, the site of greatest tenderness at metatarsophalangeal joint of great toe

severe, nocturnal attack. The first two of these three attacks had been attributed to acute rheumatism This third attack lasted for two months, and a diagnosis of gout had been made by two consultants Treatment consisted of a purine-free diet, with cinchophen and wine of colchicum Each of these attacks had been associated with the sudden onset of marked redness, swelling, tenderness, and pain of the involved joints, and had been followed by complete remission Dietary habits included the eating of two servings of meat daily, of liver infrequently, and a sip of alcohol on the rarest occasions only, perhaps once in two years

The attack because of which we saw the patient began thirty hours after operation, the pain appearing first in the calf of the left leg, then rapidly descending to involve the dorsum of the foot, and settling in the left great toe, which was red and swollen to grade 2 The site of maximal tenderness was the mesial aspect of the metatarsophalangeal joint (Fig 219) No tophi

were found and no olecranon bursitis was present The value for uric acid was 8 mg in each 100 c.c. of blood and that for urea on the same basis 26 mg Two days later the right great toe became painful for a few hours then the pain subsided but it returned in acute form after two days Roentgenograms of both feet did not give evidence of abnormality The patient was soon dismissed to continue a purine free diet and interrupted courses of cinchophen The joints cleared up so that two weeks after the onset she had no swelling or redness and only slight pain on walking A month later she was entirely free of trouble with her joints.

Although tophi were absent, it hardly can be doubted that this woman had gout The diagnosis of presumptive gout is justified on the basis of the history of the repeated attacks of characteristic acute arthritis with complete remissions, and the marked hyperuricemia Thus, a rare phenomenon was presented gout affecting a woman Slocumb and Hench recently have made a review of the several hundred cases of gout seen at the clinic There were only two instances of proved, or tophaceous, gout in women, and only about a dozen other women presented criteria sufficient for a diagnosis of presumptive gout in the absence of tophi These statistics corroborate the statement of Ehrström and others that the incidence of gout among men is probably forty times greater than among women In spite of its rarity among women, when gout does affect a member of this sex, its nature and course is, contrary to the belief of some, similar to that among men

It may be significant to note that in Case V in which a relatively minor operation was performed, the acute paroxysm occurred not after a delay of three or four days, but promptly one day after operation

COMMENT

Surgical operations have not received sufficient recognition as possible excitants of gout, only a few brief comments having been made on this possibility In this connection Scudamore reported the occurrence of a gouty paroxysm after a cataract operation, the attack "evidently called forth by the influence of the constitutional disturbance from the operation" Duckworth mentioned venesection or other loss of blood and "sudden shock

to the body from injuries and surgical operations," determinants earlier cited by Garrod In considering what factors attending operation might be responsible, it is to be recalled that conditions incidental to surgical operations generally serve to relieve infectious arthritis temporarily Four factors operate to provide this benefit the vasodilation caused by anesthesia and postoperative fever, the relief from trauma by rest in bed, and perhaps dietary regulation

One might expect that these factors incident to surgery would operate with similar beneficence in cases of quiescent or chronic gout Experience indicates the contrary Closer attention to the nature and character of the postoperative forms of arthritis seen by us fortified the impression previously gained that when, without any apparent reason, acute arthritis complicates operation, on men at least, the possibility should be seriously considered that it represents an acute, generally short, bout of gout If it is the initial attack, the clinical suspicion of gout lacks the support generally provided by a suggestive past history A later attack may occur without arousing special concern if patients and their physicians have been under the impression that they had previously acute or chronic infectious arthritis On the basis of these experiences we feel that our axiomatic generalization to "suspect gout in cases of acute postoperative arthritis, especially in males," has served us well

As yet little or nothing is known about the balance struck in the intestines between formation and absorption of uric acid and destruction and elimination of uric acid Perhaps the acute attacks which follow surgical procedures occur only when there is a none too secure or favorable balance in purine metabolism Perhaps they result from increase in endogenous urates through abnormal postoperative destruction of bodily tissue, as Llewellyn suggested, or by some postoperative disturbance of physiologic processes which interferes with the alleged uricolytic and uricogenic properties of intestinal bacteria

Diagnosis —It is sometimes easier for a layman friend of the patient to suspect the presence of gout than the patient or his

physician Of these five patients two (Cases I and III) came to the clinic with the previous diagnosis of bunions, chronic infectious arthritis or thrombo-angiitis obliterans (Buerger's disease) A third (Case V) had received a diagnosis of acute rheumatic fever in the first two attacks involving knees and wrists, and did not receive the diagnosis of gout until it occurred "classically" in the great toe in the third attack In the other two cases a diagnosis of gout was made during the first attack of podogra In our general experience only a small percentage of these patients come here with the diagnosis of gout

In only 12 per cent of our recent series of 100 typical cases of gout had this disease been considered prior to admission at the clinic [19] The basis for early diagnosis is found in several features The most consistent is a history of short attacks of arthritis, with or without hyperuricemia The attack usually is repeated and each is followed by complete remissions Although in the initial or subsequent attacks the great toes are more frequently affected than other parts elsewhere, the feet may long be spared, making the suspicion of gout seem unfounded When the initial attack occurs (as in Case V) in the wrist and knee, without involvement of the feet, suspicions are not aroused and the diagnosis of gout is undoubtedly delayed

In these five cases, as in our larger series, little or no support for the suspicion of gout was gained from the family history In none of these five cases was there a history of gout in the family Moreover, two of the five patients used alcoholic drinks little or none, three of them had no liking for foods in which concentration of purines is high, three of them ate meats only in moderation On the other hand, such attacks as were experienced by three of them were related to special excesses of food and drink

Provocative tests of many sorts have been devised to aid in the diagnosis in doubtful cases An excess of purines is given over short and over long periods of time These tests have a certain usefulness if the results are positive, but often no clinical disturbance is produced Even patients with proved gout often are undisturbed by excesses of food and drink, and one must

conclude that dietary excesses are not a primary cause of gout but are merely one of a number of excitants which may provoke the quiescent disease to explosive activity

Four of the five patients whose cases are reported were Jews This is probably a coincidence, and certainly does not represent an established incidence, although Duckworth felt that gout was seen especially among Jews, possibly because of consanguinity and the factor of heredity Our general experience does not confirm this unexpected racial preponderance The peculiar seasonal influence exerted in spring and autumn is illustrated in these five cases April to June apparently is the time of greater incidence

In all five of these cases in which the metatarsophalangeal joint of the big toe was involved, the site of maximal tenderness was the mesial portion, rather than on the top or bottom Lambert and Williamson have used this as a point in differential diagnosis of podogra with and without gout In nongouty arthritis the greatest tenderness is generally found on pressure from below the joint, not from the side In gout the maximal soreness is found on the mesial aspect This may be a suggestive point in early diagnosis, but perhaps needs the support of other clinical data

In this group of five cases, roentgenologic examinations of the joints was of little help Results were negative in two cases, there was bursal thickening, or periarticular swelling in two others, and the appearance was characteristic of gout in only one This is in accord with our general experience as to the unreliability and lack of specific value of roentgenograms in other than late gout

The complete and rapid recovery experienced by the patient who in eight days after having severe pain was able to stamp his foot vigorously but painlessly is characteristic of early attacks, treated or untreated The full degree of recovery recalls the classic remark of Aretæus "A person subject to gout has won the race at the Olympiac games during the interval of the disease"

Treatment—During an acute attack of gout the patient is

placed on a purine free diet, the joints are put at rest, and heat is applied Sometimes heat aggravates the pain but cold compresses give relief During the first two or three days of an attack, wine of colchicum is given every three to four hours in doses of 15 to 20 minims, but its administration is discontinued, after two or three days, or sooner if diarrhea is provoked This may provide marked analgesia, although it does not apparently affect the uric acid content of the blood or urine If pain is not relieved, a few doses of morphine may be necessary Cinchophen is given in doses of 7 5 grains (0 5 gm) from three to five times daily Weintraud has urged that during administration of cinchophen alkalies be given to prevent the possible deposition of urates in an acid urine in the presence of a suddenly increased concentration of urates He suggested giving 15 gm of sodium bicarbonate the first day and from 5 to 10 gm on succeeding days This should not be taken, however, at the same hour as the cinchophen Ample quantities of fluid, from ten to twelve glasses, and a portion of sweetened fruit juice, are also given daily Generally the attack subsides fairly promptly In a few prolonged attacks, injection of small doses of foreign protein has hastened recovery

Until the attack subsides the patient is kept on a purine free diet If a patient's symptoms subside, and the value for uric acid of the blood recedes appreciably, the patient is soon permitted to eat foods of moderate content of purine, at first every other day, later once a day

It is a great mistake to discontinue treatment when the attack has subsided Interval treatment is essential to prevent further attacks of gouty arthritis, and, what is probably more important, to prevent a progressive visceral lesion in the kidneys or elsewhere For although the joints seem subjected to periodic and recognizable insult, to which they strongly react, it is possible that other tissues, particularly the kidneys, are more or less continuously subjected to the toxic agents of gout, but for a long time they give no symptoms It is strange how often interval treatment is neglected entirely This seems as irrational as it would be to help a patient to overcome a period of

diabetic coma, and then to dismiss him to shift for himself until the next inevitable period of crisis

When the acute attack has fully subsided interval treatment is outlined to be continued more or less indefinitely The diet low in purines is continued, involving maximal reduction in intake of foods in which purines are in high concentration, complete abstinence from alcoholic drinks, and meat once a day Von Muller has advised one or two meat-free days each week according to the severity of the case If renal function is normal, a purine-free diet high in protein, is advisable, for Folin, Berglund, and Derick demonstrated that more uric acid is eliminated on this diet than on a purine-free diet, low in protein Milk, eggs, cream, and cheese are the foods, purine-free but high in protein, used to increase the allowance of protein

Part of the interval regimen consists of periodic treatment with cinchophen Of this drug, 7 5 grains (0 5 gm) are given two or three times a day, three consecutive days a week, but not on the other days The patient is instructed to take a large amount of fluid and sweetened fruit juice daily and alkali according to the recommendations of Weintraud, which have been given In accordance with present knowledge of toxicity of cinchophen these precautions will prevent, if prevention is ever possible, serious hepatic or other injury To date, at least, we have not witnessed significant ill effects of cinchophen among our patients with gout If, because of previous hepatic disease, treatment with cinchophen seems inadvisable, salicylates can be given as an alternative, in similarly interrupted courses

Estimations of the value for blood uric acid, every two to four months, are advisable If the patient has remained free from attacks for several weeks or months, judicious retrenchment in treatment by drugs and diet are permissible

To prevent exacerbations, attention is given to elimination of trauma, and patients are cautioned to avoid unusual excesses in golf or walking, and to avoid use of tight shoes or other traumatizing agents Moderate exercise is to be encouraged Foci of infection are eliminated, not because there is much to indicate that gout is infectious, but because focal infection,

tonsillitis, acute dental abscesses, and so forth seem to provide sufficient disturbance in metabolism to precipitate certain attacks If persons who have gout or who are suspected of being susceptible to attacks of it must undergo operation, a few days of preoperative care seems indicated, employing a diet low in purines and a few small doses of cinchophen

Although the current treatment of gout as here outlined is empiric and cannot be termed really specific, its results have been gratifying to the majority of our patients Particularly if treated before the stage of chronicity, they have been able to cut down markedly or to escape entirely further paroxysms

CONCLUSIONS

Of the determinants of acute attacks of gout the following seem of most frequent occurrence dietary excesses, surgical operations and other trauma, often of minor degree The cases presented here justify the view that in the presence of an attack of acute arthritis which comes on unexpectedly following a gastronomic spree, after an operation, or after trauma which is much less significant than the results thereof, gout should be suspected until the condition is proved to be some other form of joint disease

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EXTRAPULMONARY BRUITS FROM ARTERIOVENOUS FISTULA OF THE INTERCOSTAL VESSELS REPORT OF TWO CASES

PHILIP S HENCH AND BAYARD T HORTON

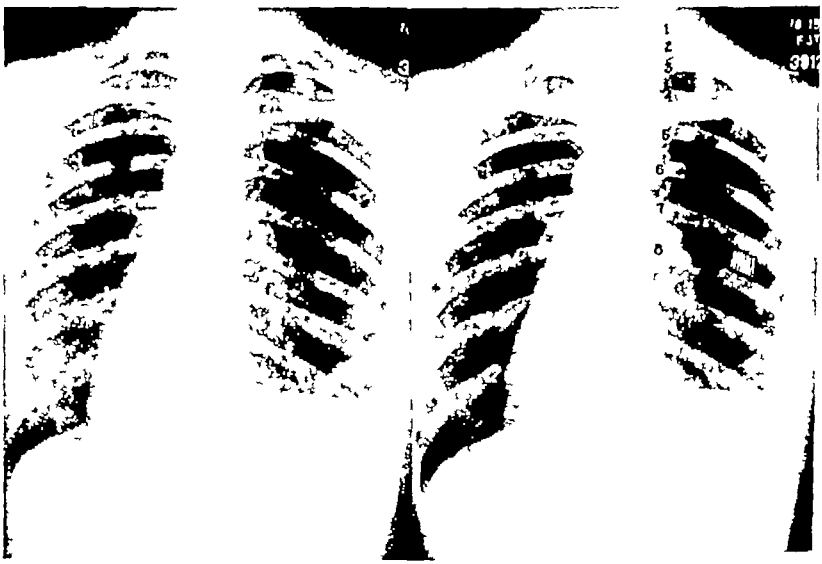
Congenital arteriovenous fistulas have been regarded as rare anomalies and even as late as 1930 Dean Lewis, in a critical review of medical literature, was able to collect only twenty-four cases of this vascular disturbance To this number he added six cases of his own, making a total of thirty Since then Horton has reported twenty-three cases of arteriovenous fistula which were observed at The Mayo Clinic between June 1929, and May, 1931 So far as we are aware the fistulas in all of these reported cases have involved vessels of the extremities, neck, or head, and no cases have been reported of primary involvement of the intercostal vessels or of the vessels of the abdomen In the past year we have observed two patients with what appear to be congenital arteriovenous fistulas of intercostal vessels In each case there was an extra pulmonary bruit, but the additional usual signs and symptoms of arteriovenous fistula were absent The vascular abnormality in each case was found incidentally in the course of examination for unrelated disease

REPORT OF CASES

Case I.—A woman thirty years of age, was brought to the clinic August 14 1932 suffering from an acute attack of appendicitis At the age of four teen years she had had pneumonia following which she had chronic bron chitis for a year but no hemoptysis or night sweats. In 1922 in the course of a general examination at the clinic, a roentgenologic diagnosis was made of tuberculosis of both upper lobes probably active on the left. There was no clinical evidence of activity however She went to a sanitarium for a while but was dismissed for lack of evidence of activity of the pulmonary lesion.

In the course of examination of her lungs prior to anesthesia a peculiar noise was heard over the right side of the thorax, in the seventh intercostal

space posteriorly, just beneath the lower tip of the scapula Registering well over the normal breath sounds, this noise was so loud that the examiner removed the stethoscope, believing it an extraneous sound, the source of which might be in the room On continuance of the examination a loud bruit was heard, crescendo-diminuendo in type, synchronous in time with the pulse rate and persisting through the cardiac cycle The quality of the bruit was not changed when the patient held her breath or breathed forcibly The bruit was heard over a very circumscribed area, 3 cm in diameter, just below the inferior tip of the right scapula There was no palpable thrill When the patient leaned forward or to the left, thus widening the intercostal space, the sound was heard better, but it became faint when she leaned back or to the



A B

Fig 220 —Case I A, Unretouched roentgenogram, view taken from the back. B, Roentgenogram retouched to show site of bruit from arteriovenous fistula in the seventh right intercostal space posteriorly

right The latter apparently tended to compress the intercostal vessels and to obliterate the abnormal arteriovenous communications sufficiently to eradicate the bruit Bradycardia was not produced by pressure over the site of the bruit The lungs and vascular system otherwise seemed entirely normal Her pulse rate varied between 70 and 85 beats each minute while she was in the hospital Our impression was that she had a small congenital arteriovenous fistula involving the vessels of the seventh intercostal space During her convalescence from appendectomy, the thorax was examined on several occasions but we could not hear the bruit at all

In October, two months after appendectomy, she returned to the clinic for reëxamination At this time the bruit was again very distinctly heard,

and was situated in the same position as before. At this time the sound was not quite as intense as on first examination and was lessened on deep inspiration probably due to impact of the lungs against the thoracic wall The bruit was accentuated when the patient leaned to the left, and diminished when she leaned to the right There was no evidence of collateral circulation or change in the cutaneous temperature of the thoracic wall. The vascular system otherwise was apparently normal The heart was not enlarged and cardiac murmurs were not present The blood pressure was 110 mm of mercury systolic and 80 diastolic and was equal in both arms There was no evidence of intrapulmonary disease A roentgenogram of the thorax gave evidence of a small pleuritic lesion at the right costophrenic angle, but not of abnormalities of the ribs such as erosion (Fig 220) Fluoroscopic examination of the thorax also gave negative results.

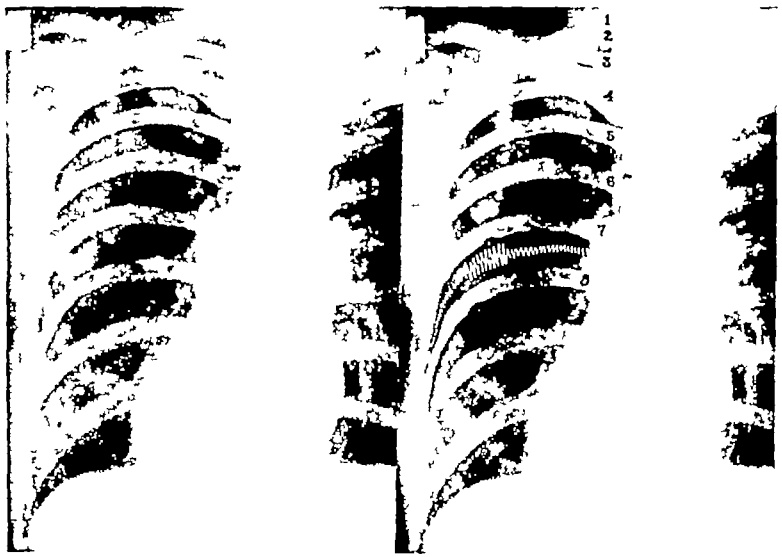
Comment on Case I—There was no history of injury to account for the presence of such an abnormal vascular communication and therefore a presumptive diagnosis of congenital arteriovenous fistula involving the vessels of the right seventh intercostal space was made. We can give no definite explanation of the fact that the bruit was present only intermittently

Case II.—A housewife aged thirty three years came to the clinic Feb ruary 13 1932 complaining of weakness and painless jaundice In January after she had experienced three weeks of bearing down pains exhaustion insomnia, anorexia and a septic type of fever the product of a pregnancy of two months duration was *removed from her uterus by her home physician* A stormy, febrile course followed including the onset of deep jaundice and the appearance of bile in both urine and feces It was at this time that she was brought to the clinic. A diagnosis of severe toxic subacute hepatitis probably with subacute yellow atrophy of the liver was made on the basis of extensive studies of the blood and urine, and of hepatic function the details of which are omitted for they do not concern the feature under discussion

On physical examination besides the jaundice enlargement of the liver and of the spleen was noted Examination of the heart and lungs gave negative results but along the superior border of the eighth left rib extending from the spinal column around into the axilla and anteriorly in the same interspace to the costosternal juncture, there was a loud to-and fro hum. The bruit was loudest just below the inferior angle of the left scapula but was audible both anteriorly and posteriorly although it was confined entirely to the one interspace. There was no appreciable local alteration in cutaneous temperature. With fever and jaundice she had a high pulse rate and hypotension There was no evidence of other local or general disturbance of circulation The heart was not enlarged Roentgenograms of the thorax gave evidence of scalloping of the border of the seventh and eighth left ribs, with some narrowing of these ribs in the axillary line. The scalloping of the seventh rib was slight that of the eighth was much more marked (Fig 221)

There was no such abnormality on the right side, and the roentgenogram of the lungs was negative The Wassermann test was negative

After prolonged treatment for hepatitis and after a stormy convalescence, she made an unexpected and remarkable recovery, the jaundice clearing entirely In November, 1932, her physician at home reported that she was gaining weight and doing a moderate amount of housework, the bruits persisted unchanged



A B

Fig 221 —Case II A, Unretouched roentgenogram, view taken from the back. B, Roentgenogram retouched to show site of bruit from arteriovenous fistula in seventh left intercostal space, and scalloping of the margins of the seventh and eighth ribs

Comment on Case II —Two years before her admission the patient was in an automobile accident and jumped from the car Although she was found lying on her left side, she had no bruises and no pain of the thoracic wall She had had no other accidents to account for the abnormal vascular condition, and therefore a diagnosis of congenital arteriovenous fistula, involving the left seventh intercostal artery and vein was made

GENERAL COMMENT

The vessels of the seventh intercostal space were involved in both cases, in Case I, those on the right and in Case II, those on

the left. The quality of the bruits was identical in both cases and was of the type characteristically observed in arteriovenous fistulas involving vessels in extremities, that is, a continuous bruit, heard throughout the cardiac cycle, and accentuated with each systolic thrust. There were no other local signs or symptoms to indicate the abnormal arteriovenous communications and systemic manifestations were not present. The reaction of bradycardia to pressure over the affected vessels was absent in both cases There was no demonstrable cardiac hypertrophy, such as one frequently sees in cases of congenital arteriovenous fistula This was due to the fact that the fistulas were probably too small to produce systemic effects There was no evidence of increased local elevation of temperature The erosion of the margins of the seventh and eighth ribs in Case II suggests the type of lesion which one would expect from long-continued pressure on ribs from abnormally pulsating vessels such as obtain in congenital arteriovenous fistulas A study of the oxygen content of the adjacent veins in these areas would have given positive proof of the presence or absence of abnormal arteriovenous communications, but we were unable to carry out such estimations and for that reason the diagnosis in either case is presumptive, not absolute

Extrapulmonary bruits of the type encountered in these cases should be of particular interest to internists who specialize in diseases of the thorax. Lemon, who saw these cases in consultation, stated that he had never before, during twenty five years of specialization in pulmonary diseases, heard this type of bruit over the thorax. We do not know whether any significance can be attached to the fact that the intercostal vessels in the seventh interspace were involved in each instance We know of no embryologic reason why the seventh intercostal vessels should be particularly involved It is impossible to say whether these lesions will continue to develop and later produce additional local and perhaps systemic effects No attempt at treatment was made in these cases, but the situation of the abnormality would seem to indicate that surgical treatment, if ever necessary, could probably be carried out successfully

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INDICAN IN THE BLOOD A TEST OF ACTIVITY OF RENAL FUNCTION

NORMAN M KEITH AND E G WAKEFIELD

Indican, or indoxyl sulphate of potassium, is one of the so-called conjugated or ethereal sulphates often found in the urine of persons in good health This substance in the blood has been rather extensively studied by European investigators who generally agree that there is indicanemia in uremia This is an interesting observation to us in the light of our work on the concentration of inorganic sulphates in the blood in renal insufficiency, uremia, and the so-called uremic acidosis

Sulphates are usually increased in the serum in renal insufficiency before there is an elevation of blood urea, creatinine, or lowering of the excretion of phenolsulphonphthalein In about half of the cases serum sulphates are increased before there is inability to concentrate urine to a specific gravity of 1 025 As the renal insufficiency progresses, sulphate concentrations rise However, the increase in sulphates usually is not significant in the so-called renal acidosis In 1930, Momas and Shapiro studied the indican of the blood in 104 cases of severe renal insufficiency and without exception indicanemia announced the presence of or the approach of uremia, although the actual quantity of indoxyl sulphuric acid was small, from 2 5 to 5 mg for each 100 c c. of blood

We shall compare here the indican, inorganic sulphates, creatinine, blood urea, urea clearance and the phenolsulphon phthalein excretion in the urine to see what correlations can be made of these as tests of the renal function Indican was determined by the method of Haas-Jolles given by Volhard and Becher Blood urea, creatinine, and excretion of phenolsulphon phthalein were determined by the usual methods The test of

TABULATION

Case	Age, years and sex	Serum indican, grade	Blood creatinine, mg per cent	Phenolsulphon phthalein, per cent	Serum sulphate mg per 100 c.c of blood	Blood urea mg per 100 c c of blood	Standard blood urea clearance c.c cleared per minute
1	54, M	0	1 6	30	5 6	30	24 0
2	31, M	0	1 7	60	6 2	28	23 0
3	57, M	0	1 8	35	6 8	42	16 0
4	70, M	0	2 2	70	8 5	40	16 0
5	42, M	0	1 5	50	5 6	36	29 0
6	43, M	1	2 3		7 6	66	
7	16, M	1	1 4	45	8 8	64	18 0
8	47, M	1	3 3	20		84	
9	55, M	1	2 6	25		80	
10	17, M	1	1 9	40	7 6	50	17 0
11	51, M	1	2 0	45	7 1	42	26 0
12	70, M	1	2 4	30		74	
13	45, M	1	1 8	45	5 2	40	42 0
14	30, M	1	2 1	40	8 3	58	20 0
15	50, F	1	2 1	20	7 4	36	26 0
16	20, F	1	2 5	40	8 4	54	8 0
17	54, F	1	2 3	30	8 5	58	7 0
18	48, M	2	3 1	15	8 2	58	7 0
19	15, F	2	3 6	15		126	
20	51, F	2	2 7	20	10 9	82	
21	26, F	2	5 4	10	11 5	86	4 0
22	29, M	2	10 1	10	27 2	144	2 0
23	42, F	2	8 4	5	9 2	114	
24	25, M	3	6 2		14 9	96	
25	49, M	3	10 8			165	
26	67, M	4	3 8	25		110	
27	44, F	4	6 4	5		124	
28	39, F	4	9 2	5	16 3	144	3 0
29	19, M	4	15 2	0		256	
30	45, F	4	13 2	0		231	5 0

urea clearance was done by the technic of Möller, McIntosh, and Van Slyke

The study was made on patients in hospital under observation and treatment for glomerulonephritis, hypertension with renal failure, pyelonephritis, and polycystic kidneys The results are shown in the tabulation In the first five cases there was no indican in the blood The serum inorganic sulphates were elevated and the urea clearances were decreased The blood urea was slightly elevated in Case 3 The phenolsulphonphthalein was low in Cases 1 and 3 The creatinine was increased in Case 4 In Case 13 there was a trace of indican in the blood with the blood urea, creatinine, serum sulphates and urea clearance normal In Case 15 the blood urea was normal In the remainder of the cases all of the tests of activity of renal function indicated distinct renal insufficiency although the excretion of phenolsulphonphthalein was 40 per cent or above in Cases 10, 11, 13, 14, and 16, and concentrations of creatinine were normal in Cases 7, 10, and 13 In general, there was no definite quantitative relationship between any of the substances determined Such findings illustrate an important fact which we wish to emphasize here. Tests of activity of renal function supplement but do not supplant one another

COMMENT AND SUMMARY

Estimation of indoxyl sulphuric acid concentrations in the blood are of definite value as supplementary tests of renal function Much work has been done on the significance of indican in the blood, but here we shall refer to that done by Luvierato and Simeneto, who made a rather extensive study of indicanemia, their work indicates that indican occurs in the blood of normal persons up to 0 64 mg for each 100 c.c. of blood The indican content of the blood is influenced by the use of purgatives and narcotics Indicanemia is increased by intestinal obstruction, chronic suppuration or infections of long standing and in hepatic insufficiency However, Luvierato and Simoneto agree that indicanemia is most marked in cases of renal insufficiency

This study shows that early in renal insufficiency more information concerning activity of renal function is obtained by the urea clearance and the serum inorganic sulphate determinations rather than by indican in the blood Definite elevation of the indican in the blood is somewhat comparable to elevation of the creatinine in the blood They are more of prognostic than of diagnostic significance

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SEDIMENTATION OF ERYTHROCYTES IN ADDISON'S DISEASE

GILES A KOELSCHE

Little has been written concerning the rate of sedimentation of erythrocytes in Addison's disease In 1927, Bonilla and Moya reported twenty four cases in which the sedimentation rate was very rapid They asserted that the procedure had distinct diagnostic value in certain instances in which the clinical syndome was atypical Recently, these investigators have concluded that the test has considerable prognostic value They expressed the belief that the suprarenal involvement is directly proportional to the rapidity of sedimentation, although the cause is not well understood As substantiation of this hypothesis, they adduced the following experiment Unilateral suprarenalectomy was performed on each of two patients who had epilepsy, as a therapeutic endeavor against the convulsive seizures Before operation, their sedimentation rates were 3 and 2 mm On the twenty fifth postoperative day, the rates were 46 2 and 59 mm , respectively

Various factors influence the speed with which erythrocytes settle The rate of sedimentation is directly proportional to the content of fibrin in the plasma In pregnancy, senility, and childhood, the blood fibrin is physiologically augmented The blood of anemic patients has a rapid sedimentation rate, notwithstanding its normal content of fibrin An increase in viscosity of the blood inhibits sedimentation The electric potential of erythrocytes, the cholesterol content of the blood, and changes in values for chemical constituents of the blood all have been cited as factors influencing speed of sedimentation, but none has been conclusively proved According to Rourke and

Plass, the rate is not affected by ingestion of food or by aeration of blood

The most frequent cause of Addison's disease is tuberculosis of both suprarenal glands In conning 566 case histories, Guttman found that tuberculosis of the suprarenal glands was the lesion present in 69 72 per cent In order of frequency, the other lesions found were primarily contracted suprarenal glands, amyloidosis, neoplasms, and vascular lesions A few more were listed, but are of rare occurrence Wells stated that 90 per cent of all cases of Addison's disease is due to tuberculous destruction, and 10 per cent to cortical atrophy of the suprarenal glands Rolleston averred that tuberculosis is "the only common cause of Addison's disease The others, with the exception of simple atrophy, may be considered as very rare" Necropsy in thirty-four cases at The Mayo Clinic revealed tuberculosis of both suprarenal glands in 84 per cent

In view of the evidence presented, it might be assumed that the sedimentation rate in Addison's disease would be similar to that found in tuberculosis In 1,741 cases of tuberculosis, Banyai and Anderson found acceleration of the sedimentation rate in 92 65 per cent The blood fibrin is increased in tuberculosis, depending on the amount of tissue involved, and this, together with the anemia usually present, may explain the increased speed of sedimentation in most patients with this disease Some investigators feel that this procedure has diagnostic value, and, when repeated tests are made, prognostic value, but its exact significance remains a question

The sedimentation rates of the patients studied were determined by a modification of the technic of Westergren and Rubin as described by Hunt One c c of a mixture of 0 5 c c of 1 6 per cent aqueous solution of sodium citrate, and 3 5 c c of whole blood are drawn into a 1 c c pipet and placed in a special rack designed by Westergren Two readings are recorded, one at the end of the first hour, and another at the end of the second hour The results are expressed as a sedimentation index, which represents a combination of time and distance For men, the normal values are 1 to 2, and for women are 1 1 to 3 4 The details of

the method, and the estimation of the sedimentation index, are simply and concisely described by Hunt and will not be repeated here

The results obtained in the study of five available patients with Addison's disease are summarized in Table 1 The sedi

TABLE 1

SUMMARY OF FIVE CASES OF ADDISON'S DISEASE

Case.	Sex.	Hemoglobin, gm. per 100 c.c. of blood	Erythrocytes, millions.	Roentgenograms for evidence of tuberculosis.		Mantoux test	Sedimentation index.	Present status of patient
				Thorax.	Suprarenal area.			
1	F	12 8	4 58	Positive	Negative	Positive	6 8	Dead
2	F	11 6	4 78	Negative	Questionable calcification, left	Negative	1 4	Dead
3	F	11 3	4 10	Negative	Negative	(Not taken)	12 0	Fairly well
4	F	14 2	4 49	Negative	Negative	Positive	10 0	Fairly well
5	M	11 5	4 86	Negative	Negative	(Not taken)	3 2	Fairly well

Hunt method of calculation.

mentation index was normal in Case 2, slightly increased in Case 5, moderately elevated in Case 1, and markedly increased in Cases 3 and 4 None of the group was considered to be anemic In Case 1 there were positive physical signs of pulmonary tuberculosis, and a positive roentgenogram of the thorax The chests of the other four patients were negative to physical and roentgenologic examinations The Mantoux test gave positive results in Cases 1 and 4, and negative results in Case 2, it was not performed in the remaining two cases Roentgenograms of the suprarenal areas were negative in all except Case 2, in which a suspicion of calcification in the left area was entertained

If the sedimentation rate is determined while the patient is in a crisis of Addison's disease, a normal index may be obtained due to increased viscosity of the blood as a result of dehydration Therefore, if reliable results are to be secured, the blood should be taken when the patient is free from any symptoms of crisis

It is of interest to note that the patient with a normal sedimentation index and the one whose index was moderately elevated succumbed, whereas the two with markedly increased indexes are living, ambulatory, and subjectively are normal

SUMMARY AND CONCLUSIONS

The sedimentation rate may frequently be accelerated in cases of Addison's disease The cause of the acceleration may be tuberculosis of the suprarenal glands or a tuberculous focus elsewhere The sedimentation index was of no essential diagnostic value in the cases studied because all presented typical clinical syndromes The test had no apparent prognostic value in these five cases

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SYMPTOMS AND PATHOLOGY OF THALLIUM POISONING CASE REPORTS

JOHN LANSBURY

In the last two years there has been an epidemic of thallium poisoning in the United States This has been due mainly to the introduction of a proprietary depilatory paste known as "Koremlu Cream" which has been advertised as being harmless, although it contains from 5 to 10 per cent of thallium acetate, which, if ingested, acts as a violent poison Probably most cases of poisoning from this source have occurred because the victims licked their lips after the paste had been applied in the region of the mouth, rather than from direct penetration of thallium through the skin Another source of thallium poisoning has been rat poison that consisted of grain impregnated with thallium salts [21]

Cases of thallium poisoning reported in the literature in English previous to two years ago have, for the most part, arisen from its use by dermatologists in the treatment of fungoid disease of the scalp

It is proposed to consider the pathologic changes and symptoms of thallium intoxication, and to report three cases of thallium poisoning which have been observed at The Mayo Clinic Three other cases from the clinic have been published previously [22, 23]

Thallium is one of the heavy metals which was discovered by Crookes in 1861 In nature it occurs often associated with lead, in the rarer minerals Its atomic weight is 204 4, and it is therefore between lead and mercury in the periodic table, and as might be expected has many chemical and pharmacologic properties in common with these metals

The toxic and depilatory doses of thallium salts are singularly constant both for man and animals Thus, 8 mg for each kilo

gram of body weight of the acetate taken by mouth is agreed on as being the depilatory dose, 6 mg for each kilogram of body weight as ineffective, and 10 mg for each kilogram of body weight as too toxic Munch and Ward confirmed this dosage for rats, rabbits, and sheep The minimal lethal dose for man is not known exactly but for animals it is 25 mg for each kilogram Experimenting with the intravenous administration of various thallium salts in rats, I found the minimal lethal dose by intravenous injection to be about 15 mg for each kilogram These figures all refer to the monovalent salts of thallium, such as the acetate, phosphate, iodide, and sulphate The trivalent thallium salts were found by Buschke and Peiser to be only about one-tenth as toxic as the monovalent salts

It has been constantly observed that thallium is much more toxic to adolescents and adults than it is to children, and for this reason its use by dermatologists is now limited to children less than ten or twelve years of age

Thallium, like lead, accumulates in the body if repeated small doses are taken, and it is excreted slowly Devane found it in the urine of patients two and a half months after one dose had been taken by mouth, and he quoted Dostrowsky as finding it in the urine of patients as long as forty-four days after administration I estimated, after giving repeated sublethal doses of thallium intravenously to white rats, that the drug was excreted at about the rate of 0 4 mg for each kilogram each day Thallium has been found once it has entered the body, in practically every tissue of the body, particularly in abundance in the liver and kidneys Cooper and Engman quoted Marme as having found thallium in the urine, bile, milk, tears, and saliva, also, in the pericardial fluid and gastric juices

ACTION OF THALLIUM ON THE NERVOUS SYSTEM

Dixon found that direct application of thallium salts to the sympathetic chain of the neck of the cat permitted subminimal stimuli to become effective, and, from this and other experiments, he concluded that thallium acts on both divisions of the autonomic nervous system as strychnine does on the central

nervous system This work, however, has not been repeated Omerod quoted Buschke as stating that thallium does not interfere with the action of pilocarpine, although it has marked anhydrotic effect which led to its use by Cambemale in 1898 to check the night sweats of tuberculosis Buschke pointed out that the depilatory effect of thallium is most marked on those hairs which are innervated by the sympathetic nerves the inference being that epilation is effected by way of the sympathetic nervous system This view, however has been questioned, and the present consensus of opinion is that the nervous system is not involved in depilation and that thallium acts directly on the hair follicle Ma and Mu reported marked degenerative changes in the spinal ganglia of animals following a single injection of 8 mg of thallium for each kilogram of body weight and Schneider likewise found similar changes in both central and peripheral nerves

The photomicrographs of Ma and Mu showed degenerative changes in the Golgi apparatus of cells and mitochondria of nerve cells as soon as one week after the injection of thallium At the end of the third week more advanced changes were reported, in many cases the nucleolus being eccentrically placed in the nucleus, or even being forced out of it toward the periphery of the cytoplasm Recovery began by the sixth week Buschke and his coworkers noted destruction of the axis cylinders both in the peripheral and central nerves Greving and Gagel reported fatty degeneration in the sheath and axis cylinders, also, rounding of the anterior horn cells with swelling, in experiments carried out on dogs, cats, and rabbits Similar changes were found in the various nuclei of the brain, but no changes were noted in the vegetative nervous system Cortella, experimenting with massive doses of thallium administered by mouth, found the meninges congested, and the pia thickened The cerebral vessels were surrounded by mononuclear cells, were engorged, and the intima was thickened The cortical cells were pale, contained many vacuoles, and Nissl's granules had disappeared In some cases the neurones had almost disappeared Much the same type of injury was found in the various nuclei of the brain

One may therefore conclude that thallium, even in so-called therapeutic doses, may act as a violent poison to the nervous system This is borne out by the clinical manifestations of thallium poisoning Munch and Silver quoted the report of a case by Olmer and Titan, in which thallium was recovered from the cerebrospinal fluid of a patient suffering from thallium poisoning

ACTION OF THALLIUM ON THE ENDOCRINE SYSTEM

Many authors have regarded thallium as principally a poison specific for the endocrine glands, and have expressed the belief that many of the effects obtained in chronic thallium poisoning experimentally produced are really expressions of glandular dysfunction Thus, the epilation and stunting of growth of young animals were at first thought to be due to hypothyroidism, but later work tended to ascribe the various actions of thallium to direct local injury of the tissues Thallium is known to inhibit the growth of bacteria, seedlings, and plants In support of this view, Truffi, in 1928, pointed out that the local application of thallium produces alopecia at the site of inunction, which argues for the belief that the endocrine and nervous systems could not be involved in producing this effect Baumann, injecting thallium acetate subcutaneously into animals, observed a direct pyknotic action on the nuclei of the hair follicles, testes, spleen, thymus, lymph nodes, and glands of Lieberkuhn He concluded that thallium produced, as arsenic does, generalized karyolysis which is a nonspecific metallic effect, and which is most marked in those tissues which are radiosensitive As will be seen, there can be no doubt that the various endocrine glands are severely injured by thallium, but the general toxic effects of this metal cannot be explained by injury to endocrine glands only

The testes —The effect of thallium is most strikingly demonstrated in the testes Baumann confirmed the previous report of Buschke in noting extreme degeneration of the seminiferous tubules of animals previously exposed to thallium His photomicrographs showed that the tubules were partly filled with necrotic débris, the spermatogenic cells were greatly reduced in

number, and in many cases formed only a very thin lining for the seminiferous tubules Buschke and Peiser, in 1922, stated that the testes of rats fed with thallium may be completely atrophied and free from sperm This action is analogous to that of lead, as is shown by the photomicrographs of Blair Bell which are almost duplicates of those published by Baumann, in that there is complete absence of spermatozoa and almost complete absence of spermatogonia

The ovaries.—In contradistinction to the testes there are practically no changes in the ovaries following administration of ordinary doses of thallium Leigheb reported that congestion occurs in the ovaries, but this cannot be considered a specific action of thallium, for he used massive doses which caused wide spread congestion and hemorrhage in most of the organs Buschke and Zondek, however, noted that the estrual cycle in mice was stopped by administration of thallium Zondek and Aschem proved at a later date that estrus could be reëstablished within a hundred hours by injections of extract of anterior pituitary lobe. They found the ovaries intact and concluded that thallium inhibits the production of ovarian hormone

The thyroid gland.—The action of thallium on the thyroid gland was early investigated by Buschke and Peiser who noted that young rats fed with thallium had a "cretinoid look." There is no doubt that the thyroid gland can be injured by thallium The photomicrographs of Ma and Mu revealed marked degenerative changes both in nuclei and cytoplasm, the authors stating that the colloid material altered its staining properties Mu and Hu, in further investigations, discovered lowering of the basal metabolic rate among rats that had been given subcutaneous injections of 8 to 12 mg of thallium salts for each kilogram of body weight. The lowering of the metabolic rate of two rats occurred between the fourteenth and seventy seventh days after administration of thallium, the rate being as low as 32 per cent below normal at one time The authors expressed the belief that this was due to injury of the thyroid gland On the other hand, Baumann observed no characteristic effect on the thyroid nuclei a few hours after injection of thallium When experi-

menting with white rats, I found no definite change in the thyroid glands of the few animals I examined, although they had received sublethal doses of thallium salts intravenously

The parathyroid glands —Leigheb found no change in the parathyroid glands of rats and guinea pigs suffering from acute thallium poisoning No other reference has so far come to hand, except that Buschke, in 1931, noted that cataract and iritis are commonly observed in cases of chronic thallium poisoning experimentally produced, and, by analogy to the same symptoms in hypoparathyroidism in man, suggested that this occurs through injury to the parathyroid glands He also cited rachitic-like changes in bone constantly found in growing animals which are subjected to chronic thallium poisoning as being possibly due to injury of the parathyroid glands When examining a rat treated with thallium, I found a markedly degenerated parathyroid gland embedded in an apparently normal piece of thyroid tissue The parathyroid cells were the site of advanced cytoplasmic degeneration and vacuolation, with hyperchromatic, pyknotic, and fragmented nuclear changes characteristic of acute thallium poisoning elsewhere in the body I feel, in this instance at least, that the injury to the parathyroid glands may be safely attributed to thallium, although control studies were not made

The suprarenal glands —There is general agreement that the suprarenal glands are injured by thallium, the most marked effect being the vacuolation of the cytoplasm of the cortical cells Pyknosis of the nuclei, congestion, and hemorrhage are also noted Buschke and Peiser reported that the adrenal glands of animals given injections of thallium contain only a fraction of the normal amount of adrenalin Later, Buschke and his coworkers reported also decrease in the lipoid content of the suprarenal glands

The pituitary gland —Little has been found in the literature regarding the effect of thallium on this gland Leigheb found that it shared in the general congestion following administration of massive dosage of thallium It is possible that inhibition of the rutting cycle may be associated with injury to the anterior lobe of the pituitary gland, although this has not been proved

From the foregoing it will be conceded that thallium can, and does affect the major endocrine organs in experimental animals The type of injury in general is the same, it is direct and degenerative, as is shown by nuclear pyknosis and fragmentation, vacuolation of the cytoplasm, and in more extreme cases general congestion with hemorrhage The effects of thallium on other parenchymatous organs may now be considered The injury to the spleen, thymus, and lymph nodes, as reported by Baumann, has already been noted

ACTION OF THALLIUM ON OTHER PARENCHYMATOUS ORGANS

The liver —Although thallium has been found in considerable quantity in the livers of animals to which thallium has been given, there is surprisingly little histologic evidence of hepatic injury Lewin, in 1927, found no evidence of impaired hepatic function among children undergoing treatment with thallium Baumann found no hepatic lesions in his experimental animals shortly after injections of thallium Buschke, however, reported cloudy swelling in reticulo-endothelial cells in chronic thallium poisoning, and Leigheb, again using massive doses, found hemorrhage into the hepatic cells as he did in other organs I examined several livers of rats which had received intravenous doses of thallium salts, and found only slight changes, such as cloudy swelling and patches of early degeneration, although large amounts of thallium had been used Thallium was demonstrated spectroscopically in the liver without difficulty It may, therefore, be concluded that the liver is only slightly affected by thallium.

The kidneys —The effect of thallium on the kidneys closely parallels the effect of mercury If doses have been small, diuresis has been noted, also, albuminuria. In experimental poisoning, the histologic picture is typical of so-called chemical nephritis The injury is mainly in the tubules, where epithelial cells reveal various degrees of degeneration, varying from mere cloudy swelling to fragmentation, necrosis, and complete destruction Such are the observations reported by Dal Callo, Ward, and Leigheb

in cases of acute thallium poisoning Buschke and his coworkers noted the same results in chronic thallium poisoning in experimental animals, together with some interstitial changes, although the glomeruli were unaffected I noted all these changes, and, in addition, found in some rats, patches of deeply staining purple material in the collecting tubules which exactly resembled the lesion pictured by MacCallum in the later stages of poisoning by bichloride of mercury

The gastro-intestinal tract—The gastro-intestinal tract is involved in cases of severe acute thallium poisoning In experimental animals, a blood-stained, mucoid discharge from the mouth is observed which in some cases is thick and ropy, also, there is severe diarrhea with passage of considerable mucus Ward, and also Leigheb reported stomatitis, gastritis, catarrhal, and hemorrhagic enteritis with hemorrhage into the liver and pancreas These findings occur only in acute cases of fatal poisoning I found all these changes when thallium was administered intravenously In addition, the pancreas gave evidence of well-marked degenerative changes, although the islands of Langerhans were only slightly affected In one case there was cloudy swelling of the salivary glands with nuclear pyknosis Buschke and his coworkers noted a lowering of gastric acidity in poisoning of a human being, 10 mg for each kilogram of body weight had been taken

The lungs—To date no definite evidence of pulmonary injury due to thallium has come to light I observed slight congestion in the lungs of several rats to which thallium had been given, but this may have been due to general causes, since the animals were moribund when they were killed

The skin—Most interest of all has centered in the action of thallium on the skin, since the alopecia which thallium produces is such a dramatic and easily observable phenomenon The evidence and opinions as to the mechanism of this action differ considerably Buschke maintained that the action is through the endocrine and nervous systems, but his critics have pointed to the actual histologic changes in the hair follicles, which, they claim, can hardly be due to action through the nervous system

As already noted, Baumann found nuclear degeneration in the follicles and hair roots a few hours after administration of thallium Leigheb found degeneration which varied according to time elapsed since administration of the drug He reported atrophy of the papillæ, and degeneration of the germinal cells of the bulb and root sheath, which, in his opinion were responsible for the depilation He also found a moderate degree of atrophy of the sweat and sebaceous glands, and of the skin and sub cutaneous tissues Dixon stated that in the true dermis there is increase of fibrous tissue, the sebaceous glands being unaf fected He expressed the belief that the epilation was the result of interruption of the process of transition from the large polygonal cells to the hair forming stratified cells He stated, further, that large doses of thallium may cause complete and sometimes permanent degeneration of the hair follicles Truffi reported degenerative changes in the follicle, and sclerosis of the connective tissue in the skin The bulk of evidence would seem to favor local injury to the hair follicle as being responsible for the alopecia, rather than indirect injury through the endo crine or nervous systems The antihidrotic action of thallium has already been noted, and clinically, as will be seen later, the skin becomes thickened and scaly following thallium poi soning

Muscles and bones —Few references are made to the action of thallium on the muscles. Dixon stated that injection of thallium causes temporary relaxation of all smooth muscle, although, as will be seen later, violent intestinal cramps occur in clinical cases of thallium intoxication It is not known whether this is due to direct action on the intestinal musculature or to nervous stimulation I examined a few skeletal muscles from rats which had received sublethal doses of thallium intra venously The degree of injury was variable, and seemed to occur in patches In the more extreme examples, there were hemorrhage between the fibers, loss of striation, failure of the cytoplasm to stain, and some nuclear pyknosis

The blood —There are conflicting reports as to the effect of thallium on erythrocytes Generally, in reports of cases of

thallium poisoning anemia is not mentioned Testoni boldly asserted that thallium acetate does not provoke lesions of the erythrocytes of children or animals Erythropenia has been reported in a case of chronic thallium poisoning Buschke and his coworkers, reported many reticulocytes in chronic experimental poisoning, but did not mention anemia Leigheb, using massive doses, found reduction in the number of erythrocytes in animals I found no appreciable change in the number of erythrocytes in rats given thallium phosphate intravenously One feels safe in concluding that in the average clinical case of thallium poisoning, anemia does not play a part However, changes in leukocytes are frequently reported, both in clinical cases and in experimental animals A moderate degree of leukocytosis is found, with relative increase of the mononuclear cells At a later stage, there may be eosinophilia

RECOVERY OF EXPERIMENTAL ANIMALS FROM THALLIUM POISONING

Most animals recover fully if they have been given thallium in "therapeutic" doses, namely not more than 8 mg given by mouth for each kilogram of body weight, even in larger doses recovery appears to be possible Thus, the testes have been shown to return to normal, the hair to grow again, the lipoid content of the skin and adrenal glands to return to normal, and the rutting cycle to be resumed Microscopically, lesions of the thyroid gland and central nervous system have been shown to be slowly repaired, and, physiologically, the basal metabolic rate has returned to normal Thus, it would seem that in milder forms of intoxication, the effects of thallium are reversible, although, when severe injury has taken place, recovery may never be complete Thus, the growth of young animals may be permanently stunted, vision may be permanently lost, and the skeleton may be permanently deformed The question of clinical recovery will be considered later

Before turning to the symptoms of thallium poisoning in man, a peculiar property of thallium salts may be mentioned Dixon first noted that small doses of thallium acetate would

stimulate the growth of hair in shaved areas of animals whereas it caused hair to fall in other areas on the same animal Cooper and Engman, in 1931, studied the effect of small doses of thallium acetate on growth of the hair They reported that when doses of 4 to 6 mg for each kilogram of body weight were given intraperitoneally the rate of growth of hair in shaved areas of rats was increased 18 per cent. They quoted Abramowitz as having noted growth in the bald patches of alopecia areata three weeks after the patient had been given by mouth 3 mg of thallium acetate for each kilogram of body weight Buschke and Davis also noted favorable results from the use of small doses of thallium acetate in alopecia areata

SYMPTOMS OF THALLIUM POISONING

For purposes of classification, cases of thallium poisoning may be divided into acute and chronic forms, although, practically speaking, the line of demarcation between the two types is ill defined, both conditions having many features in common Thallium intoxication is usually seen in acute, subacute, or recurrent forms, and the type of symptoms would seem to be as much determined by the severity of the intoxication as by the length of time over which the metal has been ingested The commonest and mildest form of thallium poisoning encountered is that among patients in dermatologic clinics, in which thallium is given by mouth as a depilatory in fungoid diseases of the scalp In the ordinary course of events, the thallium in the whole dose of 8 mg for each kilogram of body weight is given at once in sweetened water by mouth, and nothing happens until about two weeks later, when the hair of the scalp falls out completely The body hair is only slightly affected, the eyebrows and lashes scarcely at all

Even under carefully controlled conditions, toxic effects are reported Thus, Dowling observed mild pains in joints, drowsiness, and anorexia in 90 per cent of his cases Firth noted in his cases roughening of the skin on the extensor aspect of the forearms and the outer sides of the legs, which developed about ten days after administration of the metal Smith, in a series of

children treated for fungoid diseases of the scalp, noted mild pains in the legs, pallor, and anorexia in several cases

However, certain persons appear to have an idiosyncrasy for thallium, and in its routine use for dermatologic purposes, cases of more severe poisoning are occasionally reported Those of Mu, Frazier, and Smith are illustrative These may be considered representative cases of moderately severe acute thallium poisoning The onset is with pain, and weakness in the lower extremities Paresthesia and hyperesthesia occur in arms and legs, but these symptoms are usually more marked in the lower extremities There may also be pains in the thorax and joints Varying degrees of listlessness, even to stupor, may obtain Constipation usually is present, and there are usually abdominal cramps, which may be prolonged and extremely violent

Later, the skin, especially of the lower extremities, becomes dry and scaly, with an increase in thickness resembling that seen in ichthyosis The extremities may be so warm to touch that one may wrongly suspect fever, especially as the pulse is usually rapid Elsewhere, the skin may be disfigured by purple, ecchymotic spots

Depending on the degree of intoxication, paralysis, with diminution in reflexes, may supervene, the most commonly reported sign of this type is foot-drop These symptoms usually run a course of several weeks, and epilation, which may be slight or massive, begins between the first and second week after ingestion of the toxic agent, thus providing the key to a diagnosis of an otherwise very obscure syndrome Laboratory findings in such cases are usually slight leukocytosis, mild albuminuria, and the presence of thallium in the urine Thallium is best demonstrated in the urine by evaporating to dryness a liter or two of urine, ashing the residue, and examining spectroscopically for thallium, for examination of a single specimen may give a negative result

The hyperacute, profound type of intoxication which follows ingestion of lethal amounts of thallium salts has been excellently described by Ginsberg and Niscore in their report of eleven cases Vomiting, paresthesia, and severe cramps with diarrhea developed

within twenty-four hours after eating food contaminated with thallium. Stomatitis was marked, salivation was increased, breath was foul, there were blebs on the lips, and in some cases there was a purple line at the gingivodental margin Within five days all patients showed signs of cerebral involvement The so-called chemical encephalitis, with evidence of injury to cranial nerves, choreiform movements and muscular twitchings developed Convulsions and delirium were noted in the more severe cases A rise in temperature preceded death, which appeared to be from respiratory failure

Rambar recently reported a case of fatal thallium poisoning of an infant, the disease was ushered in with thirst and polyuria He noted redness and edema of the eyelids in addition to the usual symptoms, which he quoted Fuld as observing commonly in thallium poisoning of children He also noted that the pupils were widely dilated

In the following cases, reported with the approval of the Section on Neurology, the type of poisoning which is illustrated may be described as subacute or "recurrent," since for the most part thallium was apparently ingested in small amounts over a period of weeks or months The manifestations are, in the main, similar to those found in the acute or chronic forms of poisoning but differ in that symptoms are due to localized injury of the nervous system, such as optic neuritis and foot-drop It is also striking that, in adult patients marked general injury may supervene, with relatively slight alopecia, a state exactly opposite to that found in children

The amenorrhea of one patient (Case I) is a symptom of thallium poisoning previously recorded by Buschke Three other cases from The Mayo Clinic, as has been said, have been reported elsewhere, one by Lansbury and two by Lillie and Parker

REPORTS OF CASES

Case I.—A woman aged forty six years had used Koremlu Cream for five months prior to onset of the symptoms. She had used one and a half "large jars and a sample jar of the depilatory Analysis of the cream revealed the presence of thallium. Symptoms had been of sudden onset and had consisted of a marked visual defect which the patient described as though

looking through a mist" Some months later she had noted paresthesia of the legs and hands, and had had difficulty in directing her feet and in writing She also had become slightly more emotional than usual A diagnosis of retrobulbar neuritis and peripheral neuritis was made A year later the vision had gradually improved, but there was still a residual visual defect

Case II.—A woman, aged thirty-two years, had used one jar of Koremlu Cream at intervals for three months The depilatory was found to contain thallium Shortly after she had begun the use of the cream, pains and paresthesia had been noticeable in the legs The pain had become so severe that she had been obliged to take considerable quantities of morphine for relief About two weeks after the onset she had had severe vomiting, cramps, and constipation On admission to the clinic, in June, 1931, her legs were paralyzed and she could move about only with support The eyes gave evidence of previous bulbar neuritis, but with good return of function A diagnosis was made of multiple neuritis caused by thallium or lead Thallium was not found in the urine There was wasting of the muscles of the hands and legs, and some alopecia The patient was observed again in June, 1932, at which time she was able to walk with crutches, but there was still considerable residual paralysis and atrophy

Case III.—A woman, aged twenty-nine years, for two months had used Koremlu Cream on her face On analysis the cream was found to contain thallium One month after she had begun use of the depilatory she had begun to have dull pains in the lower part of the abdomen These had become steadily worse She had become nervous and had been troubled with nausea and vomiting for six days, with severe pain in the lower extremities, and with pain in the thorax Dryness and scaliness of the skin had developed Later her legs had been so weak that support had been needed in walking The patient was observed again four months after stopping the use of Koremlu Cream and had completely recovered

True chronic thallium poisoning occurs chiefly as an occupational disease Most of the findings of subacute thallium poisoning are noted and, in addition, formation of cataract This had previously been produced experimentally in rats by Buschke

Recovery from thallium poisoning is important, both from the medicolegal and prognostic points of view It will be observed from the cases reported that complete recovery may take place even in moderately severe cases of thallium intoxication, and that improvement in the lesions of the peripheral nerves may continue over a period of many months However, extended observation will be necessary before it can be hoped that this recovery will proceed to completion

SUMMARY

It has been pointed out that thallium is a violent metallic poison which lodges in, and injures, practically every tissue in the body In nonfatal cases of poisoning of human beings the effect of ingestion of the thallium gives rise to symptoms which are predominantly referable to the central and peripheral nervous systems It is probable that many of these lesions may be permanent The use of thallium, even in carefully supervised therapeutic doses, is not a safe procedure.

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THE ASSOCIATION OF MULTIPLE HEPATIC ABSCESSES AND CHRONIC ULCERATIVE COLITIS

JOHN LANSBURY AND J ARNOLD BARGEN

Hepatic abscesses commonly complicate amebic dysentery and amebiasis James, in a series of 186 cases of amebic infestation in which necropsy was performed, found abscess of the liver in ninety five Brown, in a series of 1,101 cases of amebiasis, observed at The Mayo Clinic, found eighteen cases of hepatic abscess It is strange, therefore, that in as severe a disease of the large intestine as chronic ulcerative colitis, we should see only one case of hepatic abscess among 1,333 patients Theoretically, one might expect this complication often, since the portal system, draining the intestine, delivers blood to the liver If other cases of such infection have occurred, the evidence of hepatic injury has not been grossly demonstrable

REPORT OF A CASE

A Jewish youth aged eighteen years came to the clinic November 16 1926 Ulcerative colitis had developed when he was sixteen years of age The onset of symptoms had been gradual movements of the bowels increasing in number until he was having as many as twelve a day The stools consisted mainly of blood pus, and mucus and their passage was accompanied by cramps. His weight fell from 136 to 86 pounds (from 61 to 39 kg) When the patient was seventeen years of age cecostomy had been performed elsewhere. Following this his symptoms were somewhat relieved his weight returned to normal and the condition of his bowel was improved for eighteen months but during all this time there was considerable trouble.

General physical examination gave negative results Repeated examinations of stools failed to reveal parasites, ova or acid fast bacilli The diplostreptococcus of chronic ulcerative colitis was isolated from the rectal ulcers. Proctoscopic examination revealed the typical picture of chronic ulcerative colitis. Roentgenologic examination revealed advanced chronic ulcerative colitis involving the entire colon Following a search for foci of infection a tooth and a tonsillar tag that were suspected of harboring infection were removed The patient was treated with specific colitis vaccine for six weeks after which his condition was considerably improved the

proctoscope disclosing the active lesion confined to the lower half of the rectum

Improvement continued, and in January, 1927, the cecal stoma was closed, and a month later the patient was dismissed, feeling well and having only two stools each day Proctoscopic examination disclosed that the rectum was healed throughout Treatment with vaccine was continued

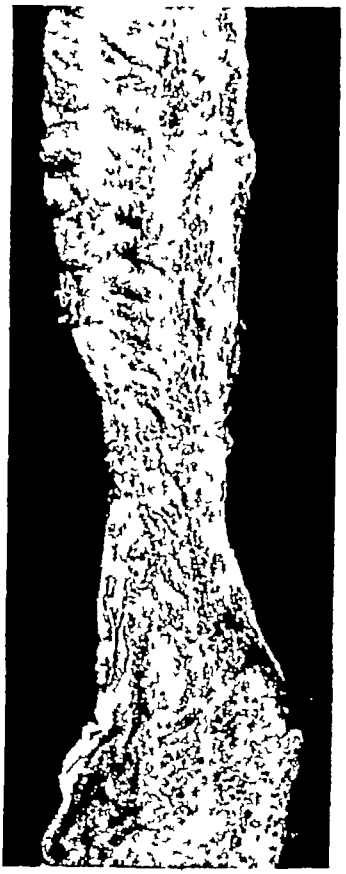

Fig 222 —Extensive denudation of the mucous membrane of the colon caused by massive ulceration The wall is greatly thickened

In January, 1929, the patient returned to the clinic because he was having seven rectal discharges a day, a condition which had gradually developed during the previous two months Examination revealed some contraction of the rectum, with slight activity of the previous lesion, also, a polyp which was removed by fulguration The general physical condition was good The patient was treated with ulcerative colitis specific antibody solution and was dismissed two months later, feeling well, having gained 8 pounds (3 kg) At that time he was having three stools daily

In July 1931 the patient had an exacerbation of his trouble and finally was forced to stay in bed again returning to the clinic in September 1931 in a serious condition He had lost 30 pounds (13 kg) was weak and rectal discharges numbered fourteen a day There was moderate secondary anemia Proctoscopic examination revealed increased activity of the lesions The temperature rose daily to 101 F Treatment with serum was instituted and there was some slight improvement but progress was not satisfactory and ileostomy was performed On the fourteenth day after operation the patient was seized with chills a septic type of fever appeared and the temperature rose twice daily to 104° F There was moderate leukocytosis and the maximal number of leukocytes was 14,000 in each cubic millimeter of blood

Fig 223 —One of the many abscesses of the liver

Physical examination gave no signs of local abscess On the eighteenth day the urine contained casts and the value for urea was 54 mg for each 100 c c of blood. Blood culture was negative. Chills occurred daily the concentration of blood urea rose rapidly Transfusion of blood given on the twenty first day after operation resulted in return of the temperature to normal but the pulse rate continued to be rapid The following day pleurisy of the right side, with effusion developed The value for urea rose to 177 mg in each 100 c.c. of blood and the patient died on the twenty fifth day The tentative clinical diagnosis was intra-abdominal pylephlebitis and pulmonary infarction with pleurisy

Necropsy revealed no changes in the peritoneum or wall of the small

intestine The wall of the large intestine was greatly thickened, and the lumen was narrowed to a maximal circumference of 4 cm (Fig 222) All evidence of haustration was lost Linear regions of thin epithelium lined the lesser portion of the colon Between them the surface was smooth, gray, and devoid of epithelium There was some enlargement of the spleen In the right pleural cavity there was some fibrinous exudate The lower lobes of both lungs contained small infarcts, the one on the right was 5 cm in diam

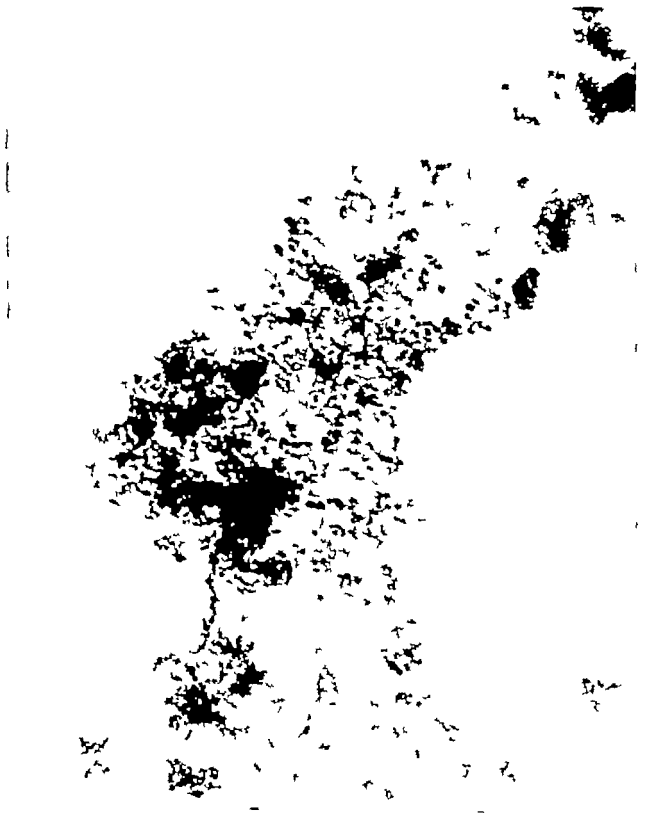

Fig 224 —Diplostreptococci in smears of the pus from the hepatic abscesses

eter, and had a necrotic center, containing liquid pus The liver was friable and contained many abscesses, 1 to 5 cm in diameter (Fig 223), some of which were coalescing Smears from these abscesses contained many gram-positive diplostreptococci which were morphologically indistinguishable from those isolated from the colonic ulcers in life (Fig 224)

Diplostreptococci grew on culture of blood obtained from the heart at necropsy These organisms were of the type isolated from the ulcers of patients with chronic ulcerative colitis

COMMENT

This case is recorded because of its extreme rarity Between January 1, 1921, and January 1, 1931, inclusive, 1,333 cases of chronic ulcerative colitis were seen at the clinic, and this is the only one in which single or multiple hepatic abscesses were demonstrable. This fact would again suggest the very fortunate detoxifying and bactericidal power of the liver

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MEDIASTINITIS

HERMAN J MOERSCH AND FRANK S KENNEDY

Perforation of the esophagus as a result of ingestion of a foreign body, with development of periesophagitis, mediastinitis, and pleuritis, always constitutes a grave surgical problem This is apparent when it is realized that the vast majority of the cases in which this complication develops terminate fatally Of five cases seen in The Mayo Clinic in the last five years, recovery has resulted in two These two cases, and one which resulted fatally have been reported, two by Vinson and one by one of us (Moersch)

Numerous factors must enter into a serious consideration of the problem, the level at which the perforation has occurred, the size of the opening in the esophagus, whether or not the foreign body has lodged within the mediastinum, its situation in that cavity, and the degree of involvement of the pleura

The literature pertaining to the subject is notably sparse, and study of the ideas expressed concerning proper treatment of these complications reveal marked uncertainty and divergence of opinion The treatment, for purposes of classification, may be divided into three types 1, surgical drainage from the outside, 2, endoscopic drainage through the esophagus, and 3, expectant treatment

Killian in reviewing the subject, gave endoscopy no place in the treatment, but advocated external mediastinotomy and thoracotomy He has shown, however, that these procedures carry a mortality of 77 7 and 80 per cent, respectively In his opinion, esophagoscopic drainage should be reserved for those cases in which there are localized abscesses in the esophageal wall King reported six cases of esophageal perforation In one case external drainage was established and the patient recovered,

whereas in another case in which, he stated, external drainage was definitely indicated but was established too late, the patient died In the four remaining cases, spontaneous drainage through the esophagus took place, the patients recovered One of these had a rent in the esophagus 1 inch (2 5 cm) long and King expressed the belief that recovery was due to the extent of the laceration The opinion he expressed was that external drainage, done early, embodies the greatest hope for these patients Kramer ardently advocated esophagoscopic drainage In Orton's series of six reported cases, five patients died without any form of mediastinal drainage, whereas one recovered with external drainage Meyersburg recorded one case of perforation from a bolus containing ground glass, drainage was established by cervical mediastinotomy, with subsequent recovery This patient was given one exposure to therapeutic roentgen rays, over the mediastinum, two days following operation Smead in reporting a case in which there was no surgical interference, advised immediate thoracotomy if perforation has extended into the pleura He added that mediastinotomy is severe and hazardous in such cases Gutteridge in a case of perforation of the left pyriform fossa instituted drainage through the point of perforation with recovery Iglauer and Ranschoff favored surgical removal of perforating foreign bodies, reporting one case in which a fish bone, which had perforated the upper part of the esophagus was removed successfully through the side of the neck Probably Seiffert has done the most extensive internal drainage, incising the posterior esophageal wall from the perforation to the depths of the mediastinal wound, with recovery

In attempting to evaluate the results of the various endoscopic procedures reported, some difficulty is experienced, for it is impossible in some cases to be sure of the degree of perforation, or to be sure whether or not the laceration and infection are limited to the esophageal mucosa

Because of the scarcity of reports of cases dealing with this subject, it seems advisable to report the two remaining cases of the five seen by us in the course of the past five years In all five cases, complete perforation of the esophagus by a foreign

body, with mediastinitis, was definitely proved by endoscopic observation of the perforation, or at postmortem examination

In one of the cases previously reported, the patient died as has been said Whether thoracotomy, with drainage of the pleural cavities and of the mediastinum might have saved the life of the patient is very doubtful The rapidity with which death ensued would seem to preclude this possibility In several cases of traumatic perforation of the esophagus, with mediastinitis and fluid in the pleural cavities, we have treated the patients expectantly and they have recovered In these cases, it was felt that the opening into the esophagus had been sealed by an inflammatory reaction, clot, or fibrin, and that removal of fluid from the pleural cavity might reopen the tear by washing away the inflammatory exudate or, that it might, by increasing motility, interfere with healing Although death occurs in a high percentage of cases treated expectantly, a sufficient number of patients recovers so that serious consideration of this method of treatment is warranted

The patient in another of the previously reported cases recovered The case truly emphasized the value of external drainage, and in certain types of cases it should be the method of choice

The remaining case of those previously reported, on the other hand, illustrated the value of the internal approach to foreign bodies in the mediastinum Although the procedure entails considerable risk, yet when it is successful, as it was in this case, it encourages one to further attempts along this line

CASES NOT REPORTED BEFORE

Case L.—A child aged three months was brought to the clinic with an open safety pin in the upper mediastinum Two months previously the infant had swallowed the pin which lodged in the upper part of the esophagus with the point turned upward An immediate attempt at removal had been made at home, in the course of which the pin was forced through the wall of the esophagus. Further esophagoscopy elsewhere on the same day demonstrated a rent in the posterior wall of the upper part of the esophagus. The child was acutely ill with swelling in the neck during the following week.

On arrival at the clinic, a roentgenogram revealed that the safety pin was in the upper mediastinum with the point turned down (Fig 225)

Esophagoscopy revealed scarring on the posterior wall of the upper esophagus but the foreign body was not visualized A second esophagoscopic examination was carried out a week later, under fluoroscopic guidance, and at this time it was demonstrated that the pin was lying outside of, and posterior to, the esophagus The point was found to be projecting for a short distance into the lumen of the esophagus No great effort was made to dislodge the pin, because of its position External esophagotomy was decided on and was carried out with the assistance of fluoroscopic guidance and esophagoscopy The pin was removed without apparent undue trauma Following the operation, increasing dyspnea developed and the child died six hours later

A B

Fig 225 —Site of open safety pin A, Anteroposterior view B, Lateral view

Postmortem examination revealed that the pin had been in the upper mediastinum, under the upper edge of the sternum The catch of the pin had rested on the apex of the right lung At the point of contact a small pulmonary abscess had formed, which had communicated with a bronchus On removing the pin the abscess was unroofed, and direct communication was established between the bronchus and the mediastinum The child died as a result of pressure from emphysema of the mediastinum

Comment on Case I —In this case, the external approach seemed to offer the greatest chance of success, although in a

previous case of similar type, referred to in a foregoing paragraph, removal of a foreign body by internal esophagotomy was successful Since the pin was lying almost entirely outside of the esophagus, the external approach doubtless caused less trauma than internal approach would have caused

Case II.—A girl aged two years was brought to the clinic with a five cent piece in the esophagus (Fig 226) The coin had been swallowed four days before. At the time of the accident the child had begun suddenly to cry and complained of pain in the throat The mother thought that the

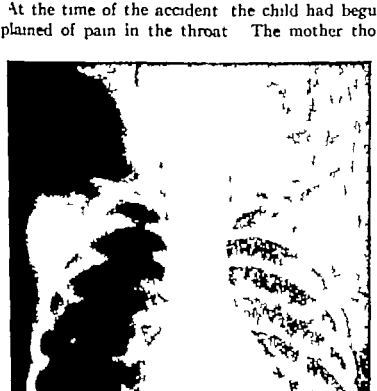

Fig 226.—Site of coin at time of perforation

child had swallowed some poisonous substance and gave her milk to drink, which she vomited She had complained of the same soreness since, and had been able to swallow only liquids

Roentgenograms of the esophagus at the time of admission revealed the coin lodged in the upper part of the esophagus Esophagoscopy revealed a considerable amount of necrotic tissue with bleeding at the introitus. The coin was visualized beyond the necrotic material Emphysema of the neck developed and external esophagotomy was decided on for it was deemed likely that the coin had perforated the esophageal wall At operation the coin was found just above the right clavicle The ulcerated perforation was closed, and a drain was left in the neck. Following the operation dyspnea and cyanosis developed and the child died a few hours later

Postmortem examination readily revealed the point of perforation, and, interestingly enough, directly opposite the point of perforation was a region of necrosis similar to that through which the coin had ulcerated The large opening which had permitted the coin to pass into the tissues of the neck had allowed the escape of esophageal content into the mediastinum

Comment on Case II —This case admirably exemplifies the problem of the logical method of procedure It can be claimed, of course, that the patient might have had a better opportunity for recovery if we had boldly inserted instruments through the opening in the esophagus and extracted the coin, hoping for proper drainage through the esophagus To us, also, looking at the case in retrospect, it seems that the external approach may have broken down any barrier that might have intervened to prevent spread of infection into the mediastinum Nevertheless, it must be remembered that the coin had perforated the esophagus and lay beneath the clavicle To reach the coin by the internal approach would have necessitated pushing the instruments through a zone of infected, necrotic material

GENERAL COMMENT

It is readily apparent that no definite rule regarding the best method of procedure can be applied in all cases of mediastinitis, periesophagitis and pleuritis, secondary to perforation of the esophagus by a foreign body That removal of foreign bodies and drainage from the mediastinum by endoscopic means are of value in dealing with this problem has been well illustrated by a case reported previously However, it is only by publication of longer series of cases, including unsuccessful as well as successful results, that in time the best procedure for this usually fatal condition may be determined Much useful help has been afforded us by reports of cases by others, and it is hoped that a review of these two cases and of the three previously reported from the clinic may be of similar assistance to others who are confronted with this problem

THE MISLEADING INITIALLY HIGH BASAL METABOLIC RATE

WILLIAM A PLUMMER, AUSTIN C DAVIS, AND EDWARD H RYNEARSON

Laboratory aids are of great value when used to supplement clinical judgment, they should seldom be allowed to supersede it Determinations of basal metabolic rate are not necessary for the diagnosis of exophthalmic goiter in a case in which markedly characteristic symptoms are present, as, for example, in a case in which there has been loss of 30 pounds in two months despite a voracious appetite, great weakness, definite intolerance of heat, and protrusion of the eyes In such cases determinations of basal metabolic rate are of value, not for diagnosis, but as helpful criteria of improvement, and as aids to proper treatment In most cases in which nervousness is the only complaint, unassociated with any of the so-called cardinal symptoms of hyperthyroidism, determinations of basal metabolic rate are not necessary to exclude the presence of hyperthyroidism Occasionally, however, a determination of basal metabolic rate in such a case is a necessary aid in ruling out the presence of hyperthyroidism Usually a reading made for this purpose effectively determines the diagnosis

There is an occasional case, however, in which determinations of basal metabolic rate tend to confuse the diagnosis rather than to clarify it In the cases to be presented, the histories and physical examinations were suggestive of the possibility of hyperthyroidism, although the characteristic syndrome was not complete, and there was good reason to obtain readings of the basal metabolic rate In each instance, on the first reading the basal metabolic rate was well above normal, and if conclusions had been based on a single determination, without due consideration of clinical symptoms and signs, an erroneous diagnosis of hyperthyroidism would have been made However, in such

cases a single determination of basal metabolic rate should never be allowed to influence clinical judgment, and the tests were repeated As the patients' nervousness subsided, the basal metabolic rates dropped to within normal limits

REPORT OF CASES

Case I —A male student, aged twenty-five years, had suffered a severe fright at the age of twelve years and since that time he had been nervous and had dreamed much at night Otherwise, he had been well and strong until four months prior to examination at the clinic, when he had become more excitable and had begun to have palpitation A diagnosis of goiter had been made, and 30 drops of compound solution of iodine had been given daily Determination of basal metabolic rate had not been made prior to the use of compound solution of iodine but after the preparation of iodine had been taken for two weeks the rate had been −7 per cent After this determination, the patient had taken compound solution of iodine intermittently He believed that his condition had improved during the first month the drug was used

On admission to the clinic, the patient reported that he was no longer conscious of the action of his heart, even when exercising, but that if he counted his pulse he would find it rapid He felt weak and tired all of the time and was unable to work He was not intolerant of heat, sweating was not excessive, his appetite was normal, there had been no loss of weight in twelve months, and there had been no change in the appearance of his eyes

General examination gave essentially negative results, except that the patient's blood pressure was 160 mm of mercury systolic and 80 diastolic, and his pulse rate, 150 beats a minute After rest in bed in the metabolism laboratory, his basal metabolic rate was +24 per cent These facts, together with the previous diagnosis of goiter, and his history, suggested hyperthyroidism Diagnosis was deferred, however, and subsequent readings, after rest in bed in the metabolism laboratory, were those given in Table 1

TABLE 1

SUCCESSIVE READINGS MADE IN METABOLISM LABORATORY (CASE 1)

Day following admission	Basal metabolic rate	Temperature, degrees F	Pulse beats each minute	Blood pressure, mm of mercury	
				Systolic	Diastolic.
1	+24	98	126	168	118
2	+17	97 6	100	154	90
5	+13	97 8	112	152	86
7	+ 4	98	122	134	58

These studies of basal metabolic rate together with further inquiry into the history indicated that the patient did not have a goiter but rather an anxiety neurosis His condition was discussed frankly with him and he was advised to do what he could to lessen his work responsibilities and worries He was warned above all not to count his pulse

Case II.—A farmer aged forty years had not felt well for the two previous years. He had noticed nothing of which to make specific complaint until three months before admission to the clinic, when he had noticed loss of strength loss of 8 pounds nervousness palpitation tremor and dyspnea About this time he also had noted increased sweating and intolerance of heat although he always had been warm blooded His only other complaint was referable to the left testis which had been painful and swollen for the last year He had not had diarrhea edema, or vomiting nor had he noted any change in the appearance of his eyes The patient's family physician had examined him a few weeks before his admission to the clinic, and because of the symptoms together with a pulse rate of 160 beats each minute had very reasonably made the diagnosis of hyperthyroidism and had begun administration of compound solution of iodine 10 drops three times daily keeping the patient at rest in bed This treatment did not produce improvement and because the physician feared that the testis might be the site of a malignant growth he referred the patient to the clinic

Examination for possible hyperthyroidism revealed tremor of the hands graded 2 However the thyroid gland seemed normal to inspection and palpation. The patient was not stimulated in appearance, he had no muscular weakness, and his eyes appeared normal In brief he did not look like a patient with definite hyperthyroidism although his history was strongly suggestive. A reading of blood pressure, taken at the time of admission was 152 mm. of mercury systolic and 80 diastolic. Two other readings of blood pressure taken the day following admission were 162 systolic and 96 diastolic and 150 systolic and 90 diastolic. Examination of the ocular fundi did not give evidence of any vascular changes associated with hypertension. In the week during which the man stayed at the clinic his pulse rate, counted in the office varied between 100 and 132 beats a minute his temperature varied between 99.2 and 99 6 F The presence of marked epididymitis and prostatitis explained both the slight fever and the swollen painful testis.

The first reading of the basal metabolic rate taken after rest in bed in the metabolism laboratory was +18 per cent and it was decided to repeat the determination after administration of a mild mixture of bromides as a sedative, but withholding compound solution of iodine or other preparation of iodine. The readings of basal metabolic rate given in Table 2 demonstrate the decline from +18 to +6 per cent, with an associated decline in pulse rate and blood pressure The readings of temperature, pulse rate and blood pressure, given in the same table, are considerably different from those made when the patient was under the tension of examination in the office.

The patient also was found to have marked dental and tonsillar sepsis Treatment consisted in assuring him that his symptoms probably were of nervous origin and not the result of a goiter and in coöperating with his

TABLE 2

SUCCESSIVE READINGS MADE IN METABOLISM LABORATORY (CASE 2)

Day following admission	Basal metabolic rate	Temperature, degrees F	Pulse beats each minute	Blood pressure, mm of mercury	
				Systolic.	Diastolic.
1	+18	99	101	132	86
3	+14	98 7	95	126	82
4	+13	99	97	130	80
7	+11	98 5	97	110	74
8	+ 6	98 2	91	104	72

physician at home in removal of foci, and treatment of prostatitis and epididymitis Subsequently the family physician reported the patient's return to health

COMMENT

These cases have similar features In each there had been a previous diagnosis of, and treatment for exophthalmic goiter, and the histories were suggestive of this disease If a single determination of basal metabolic rate had been taken as the final evidence of presence or absence of hyperthyroidism, in both cases the diagnosis would have been exophthalmic goiter Subsequent readings in each case, however, disclosed gradual and consistent decline, without the use of iodine in any form There was also an associated decline in blood pressure and pulse rate

The cases reported have been chosen at random from a large group of similar cases which have come under our observation, to illustrate the point which we wish to emphasize the need for several determinations of basal metabolic rate of patients whose initial rate is high and who do not have hyperthyroidism If the rates are consistently high this will be supportive evidence for the diagnosis of hyperthyroidism, but if the determinations of basal metabolic rate, taken on successive days, show a decline to a normal level, a diagnosis of hyperthyroidism usually should not be made

HYPERSENSITIVITY TO SOAP REPORT OF A CASE OF VASOMOTOR RHINITIS

LOUIS E PRICKMAN

The allergic nature of vasomotor rhinitis is now generally recognized, but identification of the specific allergen frequently is not accomplished, even after thorough investigation Study of the patient with vasomotor rhinitis should begin in every instance with a careful history, and with examination of the nose by a competent rhinologist to eliminate the possibility that the symptoms are due to some nonallergic condition of the nose or sinuses. In taking the history the attempt should be to bring out any possible relationship of symptoms, changing environment, contacts, ingestants, neurogenic factors, and changes in climate or temperature The history also assists in choosing the allergens to be used later for skin testing Indiscriminate skin testing with scores or hundreds of allergens is to be avoided, since the benefit to the patient is rarely in proportion to the effort expended Skin testing often assists in identification of the offending agent or allergen, but more frequently does not. In the choice of substances to be used for skin testing, emphasis should be placed on air borne substances, or substances which produce their effect by contact. Foods are infrequently responsible for nasal vasomotor symptoms, but that they may be responsible must always be kept in mind, especially when taking the history Sneezing, nasal congestion, and rhinorrhea, occurring after ingestion of certain foods, is of more importance clinically than skin tests that give positive or negative results with foods. The patient with vasomotor rhinitis need not be burdened with elimination diets in the absence of a suggestive history of sensitivity to food, unless every other method of approach to determine the cause of the patient's symptoms has been exhausted

In addition to scratch and intradermal sensitization testing, patch-testing is occasionally useful, especially with suspected substances and compounds, the ingredients of which are not known The patch test, properly used and controlled, occasionally will give confirmatory evidence of suspected hypersensitivity to soap, and also aids in choosing a nonirritating soap for the patient's use This is true, not only in instances in which the hypersensitivity takes the form of dermatitis, but also in instances in which it takes the form of vasomotor rhinitis In carrying out patch tests with various soaps, it is important to use an emulsion of soap sufficiently dilute that normal skin will not be irritated, as pointed out by Sulzberger and Wise Undiluted soap frequently will irritate normal intact skin when contact with it extends over a period of twenty-four to forty-eight hours

In the not infrequent case of vasomotor rhinitis in which all search fails to reveal the specific allergen, the patient should be advised of the possible relationship between his nasal symptoms and specific factors in his environment To assist in this, the patient can be instructed to keep a diary, in which he writes the circumstances under which exacerbations of symptoms occur Such factors as environment, contact with animals, preparation or ingestion of certain foods, or purchase of new furnishings, are only a few of the countless possible considerations which might easily be overlooked unless some systematic method for their detection is followed The use and the practical value of the allergy diary are illustrated in the following report of a case

A housewife, aged thirty-eight years, related that since the age of sixteen years, she had had nasal catarrh, with dark, mucoid discharge, but without crusts or odor For several years the condition had seemed to become more marked, and at the time of her coming to the clinic she complained of marked watery rhinorrhea with attacks of sneezing the year around As she explained, she "passed through one cold after another" The condition was associated with pains and aches, first in one portion of the head and then in another There was some associated cough, but no asthma She had used no nasal medication prior to coming to the clinic, but had undergone operations on the septum and turbinates and removal of polyps, without obtaining symptomatic relief, and radical operation on the sinuses had been advised within the month

On examination in the Section on Otolaryngology and Rhinology the effect of nasal operation with synechia on the left involving the inferior turbinate, was noted Stubs of polyps were present high up on both sides posteriorly Frank pus was present in the left middle meatus and mucoid discharge was increased throughout the nose. Roentgenologically there was evidence of a thickened membrane in both frontal sinuses both ethmoid sinuses and in the left maxillary sinus

Skin-sensitization tests to a group of common air borne and food substances gave entirely negative results. I was able however to elicit a history of sneezing and rhinorrhea following the use of a certain common toilet soap The patient also described one other possible allergic condition namely aphthous ulcers in the mouth which occurred following ingestion of English walnuts and tomatoes. There were no other leads as to specific hypersensitivity in the anamnesis. Previous changes of environment had failed to give relief from symptoms and the trip away from home when she came to the clinic was the first time she had been free from nasal symptoms for years. This observation together with a history of sneezing and rhinorrhea when using the scented toilet soap led to the suspicion that the symptoms and nasal signs probably were on a true allergic basis and due to specific irritation from an unknown substance. More exhaustive investigation from the allergic standpoint was prevented by the brief time the patient was able to be under observation at the clinic. Consequently she was advised to discontinue using the toilet soap which made her sneeze and she was further instructed to observe any other conditions in her environment that seemed to make her nose worse, and to keep a diary for this purpose

In a subsequent communication the patient stated that she consistently observed that when she used a certain naphtha soap in washing clothes and in dishwashing her nose was definitely irritated and all her symptoms returned. By substituting a different type of laundry soap she was completely free from symptoms and has remained so In explanation of the fact that she was practically free of nasal symptoms while away from home on her trip to the clinic, she volunteered the information that she had purchased a box of paper handkerchiefs to take the place of her own laundered handkerchiefs On previous trips she had taken her linen handkerchiefs and had had as much trouble as she had at home. In her words, The more I wiped my nose the more I sneezed Apparently the small amount of soap left in the handkerchiefs was sufficient to keep up the irritation

COMMENT

This case illustrates hypersensitivity to two types of soap, the one a laundry soap and the other a toilet soap, the use of which produced sneezing and rhinorrhea and secondary pains in the head Orris root to which a number of patients with vasomotor rhinitis are sensitive, is used in making some toilet soaps It is unlikely that it was the offending allergen in this instance,

however, because skin-tests with orris root were negative Also, cosmetics, which frequently contain orris root, apparently were innocuous, and a laundry soap, as well as a toilet soap, produced the symptoms

Soaps are manufactured by heating fats or oils with sodium or potassium hydroxide A great variety of vegetable oils and a small number of animal fats are used The more common vegetable oils used, in addition to that of orris root, which has been mentioned, are almond, castor, cocoa butter, cocoanut, corn, cottonseed, cucumber, kapok seed, linseed, olive, palm, peanut, and sunflower The principal animal fats used in the preparation of soap are suet, lard, wool fat, neat's foot oil, horse fat, and fish oils Less common oils and constituents of soaps are orange oil, pistachio nut oil, buckwheat meal, cinnamon oil, coriander oil, poppy seed oil, thyme oil, glycerine, and various dyes and perfumes It is almost impossible, in most instances, to obtain information as to the exact ingredients of different soaps and cosmetic products Fortunately, cases of sensitivity to soap, such as that reported, are apparently uncommon, and the use and sale of soap, therefore, do not constitute real dangers It is ordinarily not necessary to know the exact ingredients of soap to which the patient is sensitive, since desensitization need not be considered Elimination of contact with the two offending soaps, in the case reported, brought about a cure

In considering the possibility of hypersensitivity to soap, it is well to remember that a great many persons, with and without allergic sensitivity, experience definite irritation of the nose and eyes from undissolved soap powders and soap chips Persons employed at soap-making on a large scale usually require masks for protection from soap dusts Housewives also frequently complain of nasal irritation from contact with soap powders This reaction is apparently nonspecific and nonallergic, and is probably due to chemical changes occurring on the membranes when the fine soap comes in contact with normal secretions

Page and Allen have shown that when soap is introduced into the body parenterally, as, for example, under the skin or

into the peritoneal cavity, signs of intoxication appear These investigators studied the gross and microscopic changes in forty white rats following a series of seventeen intraperitoneal injections of soap given over a period of forty-one days None of the effects of these injections, which included peritoneal adhesions and minor changes in the liver, was felt to be specific

Just how often specific hypersensitivity to soap occurs clinically is not known, but it should always be looked for A search of the text books in English on allergic subjects, and of the Quarterly Cumulative Index Medicus, revealed no case of sensitivity to soap similar to the one reported here A patient sensitive to soap powder is included in a table in Rackemann's text book. This may or may not have been a case of specific hypersensitivity

Considering the universal use of soaps and soap products, and the fact that they come in direct contact with mucous membranes repeatedly, one would expect a greater incidence of hypersensitivity to soap than apparently exists If sensitivity to a soap is known or suspected, complete avoidance of contact with it is necessary, and it would further seem important to advise the patient that it may be necessary for him to use paper handkerchiefs, or at least handkerchiefs washed with soap to which he is not sensitive To overlook this might result in therapeutic failure

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PEPTIC ULCER SYNDROME WITHOUT ULCER
A FURTHER REPORT

ANDREW B RIVERS AND FRANCES R VANZANT

In a paper published a short time ago, we wrote that in the last few years we had observed an increasingly large number of cases in which symptoms usually attributable to peptic ulcer were present, but in which lesions were not demonstrable at fluoroscopy We came to entertain the belief that the symptoms in these cases were caused by other mechanisms than lesions in the stomach or duodenum, and in the paper to which reference has just been made we reported three cases which accorded with our thought that persons who were affected by this disorder were of the astute, efficient, aggressive, high tension type

The clinical and, one might say, the psychological picture presented by patients of this type was presented at length in the previous paper, and can be read therein To distinguish between true ulcer and this misleading syndrome seems of so much importance in the practice of medicine, however, that here we wish to report two cases that we have observed and then to gather together what we have learned of incidence, symptoms, and the results of investigations in the clinical laboratory

REPORT OF CASES

Case I.—A Jewish tailor aged thirty-eight years fifteen years prior to his visit to the clinic, was operated on in Russia where appendectomy and left herniotomy were performed The presenting illness began two years before admission with a dull gnawing epigastric pain coming on from one hour to an hour and a half after meals. He soon found that milk or even water would relieve him and he frequently used soda to ease the distress Occasionally he was awakened at night by epigastric pain and at times had, in addition to the distress just described a more severe pain in the epigastrium which would last but a few minutes Associated with this he

had much flatulence, and belching seemed to relieve him Fluoroscopic investigation of the gastro-intestinal tract revealed the presence of a duodenal deformity Estimation of gastric acidity by means of titration with tenth normal sodium hydroxide gave values of 124 for total and 108 for free hydrochloric acid The amount of gastric content expressed was not unusual

Subsequent investigation in the hospital revealed several facts that were important (1) It was extremely difficult to lower gastric acidity by any means, (2) frequently, whereas one glass of milk would not relieve the symptoms, two or three glasses, if taken in quick succession, would promptly dissipate the pain, and (3) the patient stated that his last exacerbation came on after changing his vocation to that of a dry cleaner, and lending some money to a friend, both of which ventures were failures He often noticed that worry or some prolonged, unrelieved difficulty would precipitate his symptoms He was thought to have duodenal ulcer, for which operation was advised At operation, however, careful examination of the stomach and duodenum failed to disclose any evidence of ulceration, the duodenum was not opened There were some adhesions across the duodenum which, the surgeon felt, were responsible for the deformity noted in the roentgenogram The gallbladder was normal After the operation another roentgen-ray examination was made The deformity in the duodenum still persisted and it was the opinion of the roentgenologist that this was caused by an ulcer

This patient illustrates that if the patient is of the nervous, intense type the usually accepted syndrome of ulcer may not be correctly diagnostic of peptic ulcer The high gastric acidity, which was controlled with great difficulty, may have been a factor in the causation of his symptoms Another rather interesting feature of this case is the fact that it frequently took rather a large amount of milk to control the distress The onset of distress following a period of worry is noteworthy The persistent duodenal deformity postoperatively cannot be ignored and there is some possibility that this is due to a duodenal ulcer

Case II —A man, aged thirty years, came to the clinic complaining that he had had epigastric distress for several years He described the distress as a burning pain which occasionally became cramp like and usually occurred several hours following a meal At times he would be entirely comfortable for two or three weeks, then he would have daily distress again On several occasions he had consulted his home physician, who had made a diagnosis of peptic ulcer He had several periods of hospitalization on a milk and alkali regimen, with relief of his symptoms Shortly before his registration at the clinic, the distress had been more persistent, and he had found it necessary to eat at frequent intervals to relieve his symptoms He had gained 60 pounds (27 kg) in a few years because of the amount of milk and cream that he had taken to control his epigastric distress

At the clinic the value for total gastric acids was found to be 88 and for free hydrochloric acid 70 There was no evidence of retention Roentgenologic investigation of the gastro-intestinal tract revealed a duodenal deformity At operation, careful examination of the exposed mucosa of the stomach and duodenum failed to disclose evidence of ulceration but there was definite evidence of pylorospasm The anterior half of the pyloric sphincter was excised and gastroduodenostomy was performed The patient in his last report said that he was considerably improved in health

This history is an excellent illustration of the symptoms usually seen in uncomplicated peptic ulcer Furthermore, the gastric acidity was high, and there was evidence of deformity in the duodenum, which subsequent disclosures indicated apparently was due to spasm The deformity was noted not only by roentgenologists at the clinic but on several occasions by others who investigated the gastro intestinal tract fluoroscopically There is one feature which might be considered somewhat unusual, that is the fact that it was necessary to resort to feeding so frequently to dispel the pain Occasionally this symptom is found among patients with peptic ulcer, but recently we have observed it more frequently among patients with ulcer symptoms who have pylorospasm but no ulcer

COMMENT

Incidence —The two cases reported were part of a material consisting of thirty two cases in which operation was undertaken because of a history suggesting a peptic lesion Thirty of the patients were males, two were females Their ages varied from nineteen to sixty-eight years, the average age being forty years. There was nothing in the family history of any significance. These patients were investigated for evidence of focal infection, four gave no evidence of it, whereas twenty four had definite evidence of infection about the teeth, in the tonsils, or in the prostate gland Investigation of blood pressures, and weight failed to disclose any definite abnormality, except that in a few instances there was decided gain in weight because of the necessity of drinking milk frequently to relieve epigastric pain

It was noted on the histories of half of these patients that they were of a very intense, nervous, high strung type In the

records of the remaining sixteen, there was nothing which would enable one to arrive at an impression regarding the temperamental type Migraine was a prominent complaint of seven patients In examination of a number of the patients who came under our personal supervision we were much impressed by the extreme degree of nervous tension under which they were living, and we arrived at the impression that it was particularly during periods of emotional instability, or following periods of prolonged work or worry, that there seemed to be exacerbations of their difficulties Approximately half of the patients themselves noted that there seemed to be a definite relationship between worry and their symptoms

Symptoms and signs —The duration of symptoms of which these patients complained was extremely variable, ranging from one month to twenty-five years The average duration was seven and three-tenths years, which certainly is ample time for the development of ulcer if such were the invariable rule among patients having a syndrome so characteristically suggestive of peptic ulcer

The general characteristics of the pain described by these patients was indistinguishable from that of noncomplicated ulcer The situation of the pain was typical, but it is significant that in most instances the pain was not referred In only two cases was there any shifting of the pain This is a point which may be of some value in differential diagnosis of these conditions since not infrequently, during severe exacerbations of peptic ulcer particularly if the lesions are of the perforating type, the pain shifts toward the right costal margin in cases of duodenal ulcer, or toward the left costal margin in cases of gastric ulcer The severity of the pain was extremely variable, ranging from a moderate, easily tolerated heart burn to exacerbations of fairly severe pain The distress usually came on as in peptic ulcer, one hour to several hours following ingestion of food In only three instances of the entire series did the pain have characteristics other than those usually seen in ulcer, and in these cases there was definite evidence of retention incident to pyloric hypertrophy or pylorospasm In half the cases the symptoms of

pain and heart burn, although appearing in the sequence characteristic of ulcer, had lost the element of periodicity, so that the symptoms were present practically every day At times in these cases there were exacerbations during which the pain was more severe In twenty-two of the thirty two cases forming the basis of this study, there was definite progression in the symptoms, in that the complaints were more persistent and more severe during the later course of the disease There is a record of nocturnal pain in about half of these cases It was amenable to the usual type of treatment instituted for patients with peptic ulcer, ingestion of food or the use of an alkali relieved it

Results of previous treatment seem of value in arriving at some diagnostic certitude in these cases Seventeen of the thirty two patients had had the type of dietary treatment which is usually followed by relief of symptoms of ulcer, but they had not derived much benefit therefrom Three patients had been temporarily relieved by milk and alkali In the remaining cases little or no benefit was obtained

At operation no inflammatory lesions were discovered in stomach or duodenum In twenty of the cases the pyloric musculature was definitely thickened Histologic study proved this to be due to simple muscular hypertrophy In a few instances there was definite narrowing of the lumen, not unlike that seen in congenital stenosis of infants In some cases the muscular coat of the entire stomach, but especially the antrum, was thicker than normal. Of the remaining twelve patients, eight had no discoverable abnormality in the stomach or duodenum, whereas four were said to have signs of simple pylorospasm

In none of the thirty-two cases was there disease of the gall-bladder or bile ducts The appendix had been removed previously, or was found to be normal, in half of the group, in the remainder it gave evidence of varying degrees of chronic inflammation.

Results of procedures in the clinical laboratory—In general, investigation of gastric contents in these cases failed to give any definite evidence regarding the presence or absence of ulcer The general average of acidity was about normal In six in-

stances the amount of material expressed suggested gastric retention On roentgenologic examination, twenty of the thirty-two patients gave evidence of some abnormality of the pylorus or the duodenum In most instances, because of the associated history, this led to the diagnosis of gastric or duodenal ulcer In a few instances pylorospasm or pyloric hypertrophy was suspected or diagnosed by the roentgenologist

PRURITUS OF JAUNDICED PATIENTS ITS INCIDENCE AND TREATMENT

ALBERT M SNELL AND HOWARD C KEYES

Among the many discomforts suffered by patients with disease of the liver or of the biliary tract associated with jaundice, pruritus is perhaps the most distressing Whereas in some cases it may be slight or transient, in the occasional case it may be almost intolerable, in fact, one celebrated surgeon stated that it is a not infrequent cause of suicide Any comfort which may be afforded such patients by palliative treatment is decidedly worth while, and in our experience is often more appreciated than a more important therapeutic contribution

Before attempting any consideration of the treatment or of the etiology of pruritus of jaundiced patients, it is necessary to review its incidence in association with various types of hepatic disease. The incidence of pruritus in jaundiced patients has been recognized for centuries, but until recently no adequate form of treatment for it has been proposed In the second century of the Christian era, Aretæus, the Cappadocian, described two varieties of jaundice and was the first to note the association of pruritus with these conditions

Murchison, in 1885, noted that itching skin with jaundice was rare, except when there was obstruction of the common bile duct. Robson stated that it was most severe in the presence of pancreatic disease It is, of course, unknown in hemolytic jaundice, and in our experience is not often encountered in the various types of intrahepatic jaundice, except those which are associated with extensive chronic hepatitis or biliary cirrhosis Among patients with choledocholithiasis, pruritus is noted in about 60 per cent Since jaundice caused by stone is frequently variable and inconstant, the pruritus often varies similarly In

stricture of the common bile duct, especially in cases of long standing, pruritus occurs with somewhat greater frequency, and in cases in which there is extensive hepatic injury may be very severe Itching is encountered in at least 75 per cent of cases of neoplastic obstruction, and is often of maximal severity In these cases pruritus often precedes the development of jaundice, a point which has been commented on by Riesman It may be said that pruritus is chiefly related to the degree and duration of biliary obstruction, although there are many exceptions to this rule Variations in the severity of pruritus cannot be correlated with fluctuations in the value for serum bilirubin nor with that for bile salts of the blood The elevations of blood cholesterol, which are known to occur in obstructive jaundice, do not seem significantly to affect the degree of itching Rosenthal stated that pruritus bears no relation to porphyrin metabolism nor to the phenomena of photosensitivity He expressed the belief that pruritus is probably related to the degree of hepatic injury, and probably that histamine or some related substance which is liberated from injured hepatic tissue may be responsible He also has considered as a possible cause that detoxification of substances which have their origin in the gastrointestinal tract may fail, and that anaphylactoid phenomena cannot be positively excluded Lichtman, in his recent paper on the subject, mentioned briefly the various theories of etiology of this condition, and the possibility of intermediary carbohydrate metabolites or abnormal decomposition products affecting the cutaneous nerves The evidence submitted by him seems to point to increased irritability of sympathetic nerve endings as the probable cause of pruritus in jaundice The whole matter may be summarized by the statement that probably some decomposition product arises from injured hepatic tissue, and increases the irritability of cutaneous nerve endings in jaundice, thus furnishing a background for pruritus

TREATMENT

Local treatment has been somewhat disappointing in the hands of most observers Colloid baths and cooling lotions are

occasionally helpful Of the latter, olive oil and lime water have been as satisfactory as any other preparation A proprietary preparation of sulphur, Mitigal, has been successfully used by Frank. General diathermy gives considerable relief in the occasional case A variety of drugs has been given internally, and occasionally good results have been described These results in some instances probably can be explained on the basis of the tendency to spontaneous variation in the degree of itching Preparations of calcium and atropine both have been advocated, but in our experience have not been helpful It has been suggested that acidosis may be a factor in the production of pruritus, and on this basis various steps have been taken to correct this condition In this connection, the use of insulin may be mentioned Klein and Holzer have mentioned the successful use of insulin in the pruritus of hepatic disease, and Malamud reported good results in five cases None of the measures just mentioned has been uniformly satisfactory in our experience, but they may be worthy of trial in the occasional case.

Recently three remedies for symptomatic relief of pruritus in jaundice have been advocated and used at the clinic with varying degrees of success The first of these, calomel, was first suggested by Eppinger, and later by McVicar and Weir It is used in divided doses of 2 grains (0 12 gm) daily, the usual plan being to administer 0 5 grain (0 032 gm) hourly for four doses The usual saline purge is omitted In certain types of cases, particularly biliary types of cirrhosis, calomel has proved to be helpful Diarrhea does not often follow its use. The method of action is, of course, unknown. In our experience it has not been particularly uniform in its action, and has been disappointing in cases of biliary obstruction with high levels of serum jaundice. The second remedy, sodium thiosulphate, was called to our attention by Buist of Brooklyn, New York It is given intravenously in doses of 0.5 gm. to 1 gm , we have been in the habit of giving it late in the day in order to insure a night's rest for the patient Like calomel, it rarely produces any systemic effect, and administration can be repeated when necessary In our experience it has been considerably more effective than

TABLE 1

Effects of Sodium Thiosulphate on Pruritus of Jaundiced Patients*

Case	Date	Age, years and sex	Duration of jaundice	Serum bilirubin mg per 100 c c	Diagnosis	Treatment	Pruritus, grade	Degree of relief	Duration of relief, hours
1		60, M	4 weeks		Stone in common duct, chronic hepatitis, and biliary cirrhosis		2		
	10/ 7			17 0		Sodium thiosulphate, 15 grains (1 gm)		Complete	10½ hours
	10/ 8			16 3		Same		Almost complete	7 hours
	10/10			10 0		Same		Moderate	No record
2		55 F	5 weeks 4 or 5 previous attacks in 5 years		Neurofibroma of common duct				
	10/ 6			8 8		Same	3	Complete	30 hours
3		59, M	7 months		Portal cirrhosis		2		
	10/13			15 0		Same		Complete	2½ hours
	11/ 5			7 2		Same		Complete	8 hours
	11/ 7					Same		None	
4		59 M	15 weeks		Carcinoma head of pancreas		3		
	10/13			7 1		Same		Almost complete	7 to 8 hours same results obtained after ten consecutive injections
5		37 F	7 weeks		Stricture of common duct				
	10/26			12 5		Same	1	Complete	2½ hours
	10/28			10 7		Same	3	Moderate	5 hours

	10/30					Same	2	Complet	3 hours
	10/31			15 1		Same	3	Moderate	4½ hours
6		66, M	9 months, inter mittent		Chronic hepatitis and cirrhosis				
	11/13			9 2		Same	1	None 4 doses on successive days produced no relief	
7		67 F			Portal cirrhosis		2		
	12/11			3 3		Same		Moderate	12 hours
	12/12			2 8		Same		Moderate	No record
8		56 M	4 weeks		Biliary cirrhosis, carcinoma of pancreas				
	12/11			15 0		Same	3	Moderate	12 hours
	12/13					Same	2	Slight	
9		58 M	10 weeks		Carcinoma of gallbladder				
	2/9			20 0		Same	2	None	
10		55 M	7 weeks		Carcinoma, head of pancreas				
	2/8			10 7		Same	2	Almost complete	8 to 10 hours
11		54 M	2 weeks		Carcinoma, head of pancreas				
	2/10			12 0		Same	3	Complete	24 hours: identical results after three consecutive injections

The cases noted in this table are not reported in the text or noted in Table 2

TABLE 2

EFFECT OF GYNERGEN (ERGOTAMINE TARTRATE) ON PRURITUS OF JAUNDICED PATIENTS*

Case	Date	Age, years and sex	Duration of jaundice	Serum bilirubin mg per 100 c c	Diagnosis	Pruritus, grade	Treatment		Degree of relief	Duration of relief, hours.	Remarks
							Intramuscularly	By mouth			
12		47 F	3 months, intermittent		Stone in common duct	2					
	2/24			5 2			0 5 mg		Complete	10	
	2/25			5 5			1 0 mg		Moderate	6	
	2/25						1 0 mg		None		
	2/26			4 0			1 0 mg		Complete	10	
13		29 F	6 weeks		Chronic hepatitis	3					
	4/ 5			11 5			1 0 mg		Moderate	6	
	4/ 6			15 0				1 0 mg two times a day	Moderate	3 to 4	Palms and soles itchy
	4/ 7			13 6				1 0 mg three times a day 1 0 mg three times a day	Moderate Complete	3 to 4 Several	
	4/11			13 0				1 0 mg three times a day	Moderate	Several	
	4/14			11 6				1 0 mg three times a day	Moderate	Several	
	4/15					2		1 0 mg three times a day	Moderate	No record	
14		62, F	8 weeks		Stone in common duct						
	4/ 4			15 0				1 0 mg four times a day	Moderate		
	4/ 7			14 7				1 0 mg three times a day	Moderate		

15	12/4	75, M	28 weeks		Stone in common duct				0.5 mg	Moderate		
	12/6			3 3					0.5 mg.	Moderate		
	12/7			3 2					0.5 mg.	Moderate		Treatment re-started for 7 days with good symptomatic relief
16		20, M	8 weeks		Epidemic jaundice	4						
	1/10			3 5			10 mg.		Complete	12		No pruritus thereafter
17		38, F	1 year Intermittent		Stricture of common duct	4						
	1/13			8 8			0.5 mg.		Moderate	12		
	1/14						0.5 mg		Moderate	18		
18		52, M	5 days		Stone in common duct	2						
	3/31								10 mg.	Moderate		
	4/1			5 0					3.0 mg. in 10 hours	Moderate	24	
	4/2								3.0 mg. in 10 hours	Moderate	24	
19		59, M	2½ months		Carcinoma hepatic duct	2						
	3/25								10 mg	None		
	3/26			15 0					10 mg. three times a day	Moderate		
	3/27								10 mg. three times a day	Moderate		
20		69, M	2 weeks		Carcinoma head of pancreas	4						

EFFECT OF GYNERGEN (ERGOTAMINE TARTRATE) ON PRURITUS OF JAUNDICED PATIENTS*—*Continued*

Case	Date	Age, years, and sex	Duration of jaundice	Serum bilirubin, mg per 100 c c	Diagnosis	Pruritus, grade	Treatment		Degree of relief	Duration of relief, hours	Remarks
							Intramuscularly	By mouth			
20	2/ 5			10 0			0 5 mg		Complete	12	
	2/ 6			13 6			1 0 mg		Complete	3½	
							1 0 mg		Complete	10	
	2/ 7						1 0 mg		None		
	2/ 8			15 0			1 0 mg		Slight	12	
	2/10						1 0 mg		Complete	9	
	2/11			15 0			1 0 mg		Complete	4	
									Moderate	6 hours additional	
	2/12			11 5			15 grains (1 gm) sulfactol intravenously		None		
							15 grains (1 gm.) sulfactol intravenously		None		
	2/13			10 0			1 0 mg		Complete	5	
	2/14						1 0 mg		None		
	2/15			10 0			1 0 mg		Moderate	6	
	2/16						1 0 mg		Moderate	6	
21		31 M	5 months		Metastatic (?) carcinoma of liver	3					
	3/31							2 mg every 4 hours	Moderate	8	
	4/ 1			18 8				1 0 mg three times a day	Moderate	12	

22		22 M	2½ months		Carcinoma pancreas	bowel	3					
	3/1				4 3			1 0 mg		Complet	5	
	3/2				5 7			1 0 mg.		Complete	2	
	3/3				5 0			15 grains (1 gm.) sulfactol intravenously		Complete	2	
								15 grains (1 gm.) sulfactol intravenously		Complete	2	
	3/8				3 4			1 0 mg		Complete	9	
	3/10				3 4			1 0 mg		None		
	3/11				3 1			15 grains (1 gm) sulfactol intravenously		Violerate	10	
								15 grains (1 gm.) sulfactol intravenously		None		
23		60, M	2 years, intermit tent		Stricture of common duct		4					
	12/7							0.5 mg.		Complete	5	
	12/8				2 7			0.5 mg.		Moderate	Indefinite	
	12/9							0.5 mg.		None		
	12/10							15 grains (1 gm) sulfactol intravenously		None		

The cases noted in this table are not reported in the text or noted in Table 1

calomel, but does not affect more than 50 per cent of patients favorably A group of selected cases of various types of obstructive jaundice in which sodium thiosulphate was used is reported in Table 1 It will be noted that the results are not always consistent even in the same case The third and most effective remedy, ergotamine tartrate, has recently been advocated by Lichtman This preparation can be given orally in doses of 1 mg three or four times daily, or subcutaneously or intramuscularly, in doses of from 0 5 to 1 mg once daily No systemic effect of any consequence was noted in our series of cases Although its action has not been uniformly successful, it has been a most helpful remedy, and the comfort of jaundiced patients has been greatly increased by its use A group of cases in which treatment was with ergotamine tartrate is presented in Table 2 We have encountered a number of patients who were not relieved by its use, and in some of these sodium thiosulphate has given satisfactory results The following cases are illustrative of some of the problems encountered in treating pruritus of jaundiced patients

REPORT OF CASES

Case I —A railroad employee, aged sixty-six years, registered at the clinic January 4, 1932 His past history was unimportant During the summer months of 1931 he had suffered from diarrhea, which had been partially controlled by a fat-free diet Late in the summer the diarrhea reappeared with increased severity, and when an attempt was being made to control the diarrhea, he suddenly became jaundiced Almost immediately severe pruritus developed, which had persisted until the time of admission

Physical examination revealed that the patient was emaciated and had obviously lost a great deal of weight He was deeply jaundiced, and all of the skin was involved by factitious dermatitis, with numerous scratch marks and large excoriations The heart and lungs were normal The abdomen was somewhat distended The liver was greatly enlarged and its edge could be felt about 10 cm below the costal margin It was hard, but did not appear to be nodular There was no ascites The gallbladder and spleen could not be felt On examination of the extremities, a large, hard tumor could be made out on the distal portion of the right femur The urine was essentially negative, except for the presence of large quantities of bile The Wassermann reaction of the blood was negative The value for hemoglobin was 13 gm in each 100 c.c. of blood, and the number of erythrocytes and leukocytes in each cubic millimeter of blood was approximately normal The stools contained practically no bile on chemical examination, and duodenal drainage failed to reveal more than a small trace The value for urea was 26 mg and

for cholesterol 273 mg in each 100 c.c of blood The value for serum bilirubin varied from 22 to 30 mg in each 100 c.c The galactose tolerance test gave negative results. Roentgenologic examination of the upper part of the abdomen and of the thorax disclosed nothing of any consequence Roentgenologic examinations of the affected femur gave evidence of the presence of a large osteochondroma Our diagnosis was carcinoma of the head of the pancreas with obstruction of the common bile duct

Because of the patient's poor condition and his age any attempt to relieve biliary obstruction by surgical measures was considered out of the question. An attempt was made, however to control his pruritus, about which he made his principal complaint January 3 at 4 30 p m 0 5 mg of ergotamine tartrate was given intramuscularly The patient had complete relief throughout the night and was comfortable until about 8 a m the next day On the night of January 4 1 mg was given by the same route but with absolutely no relief January 5 at 5 15 p m, 15 grains (1 gm) of sodium thiosulphate was given intravenously but it had no effect on the pruritus January 6 2 grains (0 12 gm) of calomel was given in divided doses with relief estimated at 50 per cent for about twenty-one hours January 7 1 mg of ergotamine tartrate was given intramuscularly and the patient was almost completely relieved for about twelve hours No drug was given on the following day and the patient continued to suffer severely in spite of local applications January 9 1 mg of ergotamine tartrate was given at 8 00 p m with complete relief for seven hours At the time of dismissal the patient was suffering from pruritus chiefly on the hands and feet his trunk being remarkably free He died shortly after leaving the clinic and at necropsy a carcinoma of the head of the pancreas obstructing the common bile duct was found.

Case II.—A contractor aged sixty four years registered at the clinic December 28, 1931 For about four weeks before his admission he had had severe, generalized itching of the skin and for about three weeks had been deeply jaundiced His stools were described as clay-colored and his urine as dark. Following the appearance of jaundice he had vague upper abdominal pain but this did not trouble him particularly

Physical examination revealed that the patient was deeply jaundiced and apparently had lost some weight. The heart and lungs were normal. The liver was palpable about 5 cm below the costal margin and the gall bladder was felt as a distended globular tumor below the edge of the liver Urinalysis, blood count and serologic test for syphilis gave negative results Roentgenologic examinations of the thorax and of the region of the gall bladder also gave negative results. The value for serum bilirubin was 21 4 mg for each 100 c.c. and the reaction was direct. In material obtained by duodenal drainage bile was completely absent and bile could not be demonstrated in numerous specimens of stool A galactose tolerance test gave negative results. A tentative diagnosis of carcinoma of the head of the pancreas was made.

While the patient was under observation in the hospital the pruritus which previously had been troublesome became considerably worse De-

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Because of the patient's poor condition and his age, any attempt to relieve biliary obstruction by surgical measures was considered out of the question. An attempt was made, however, to control his pruritus about which he made his principal complaint. January 3 at 7.30 p.m. 0.5 mg. of ergotamine tartrate was given intramuscularly. The patient had complete relief throughout the night and was comfortable until about 8 a.m. the next day. On the night of January 4 1 mg. was given by the same route, but with absolutely no relief. January 5 at 5.15 p.m. 15 grains (1 gm.) of sodium thiosulphate was given intravenously but it had no effect on the pruritus. January 6 2 grains (0.12 gm.) of calomel was given in divided doses with relief estimated at 50 per cent for about twenty-one hours. January 7 1 mg. of ergotamine tartrate was given intramuscularly and the patient was almost completely relieved for about twelve hours. No drug was given on the following day and the patient continued to suffer severely in spite of local applications. January 9 1 mg. of ergotamine tartrate was given at 8.00 p.m. with complete relief for seven hours. At the time of dismissal the patient was suffering from pruritus chiefly on the hands and feet; his trunk being remarkably free. He died shortly after leaving the clinic and at necropsy a carcinoma of the head of the pancreas obstructing the common bile duct was found.

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Physical examination revealed that the patient was deeply jaundiced and apparently had lost some weight. The heart and lungs were normal. The liver was palpable about 5 cm. below the costal margin, and the gall bladder was felt as a distended, globular tumor below the edge of the liver. Urinalysis, blood count, and serologic test for syphilis gave negative results. Roentgenologic examinations of the thorax and of the region of the gall bladder also gave negative results. The value for serum bilirubin was 21.4 mg. for each 100 c.c. and the reaction was direct. In material obtained by duodenal drainage bile was completely absent, and bile could not be demonstrated in numerous specimens of stool. A galactose tolerance test gave negative results. A tentative diagnosis of carcinoma of the head of the pancreas was made.

While the patient was under observation in the hospital the pruritus which previously had been troublesome became considerably worse. De

cember 31 he was given 0 5 mg of ergotamine tartrate intramuscularly and obtained complete relief for four hours This injection was repeated just before the patient retired, he remained comfortable throughout the night and most of the following morning January 1, this dose was repeated without benefit, and on the following day a double quantity of ergotamine tartrate, administered in the same way, failed to relieve the pruritus January 3, 15 grains (1 gm) of sodium thiosulphate was given intravenously and pro duced relief estimated at 50 per cent for ten hours On the following day, the same remedy failed to produce the slightest effect January 6, ergotamine tartrate was again used, 1 mg intramuscularly, giving about twelve hours of partial relief On the following day the same dose was almost without effect January 9, 2 grains (0 12 gm) of calomel was given in divided doses without benefit January 10 the use of ergotamine tartrate in a dose of 1 mg was entirely successful and gave complete relief for eight hours On the following day the same dose failed to give relief January 12, and again January 14, 1 mg of ergotamine tartrate gave moderate relief

January 14, exploratory laparotomy was performed, the gallbladder was greatly distended and the common bile duct was dilated to a considerable degree The point of obstruction seemed to be at the ampulla of Vater The primary lesion could not be identified absolutely, but was thought to be carcinomatous Cholecystgastrostomy was performed, no attempt to attack the obstructing lesion directly being possible The intense and intractable pruritus had completely disappeared in forty eight hours from the time of operation At the time of dismissal from the hospital, two weeks later, the value for serum bilirubin had fallen to 4 3 mg for each 100 c c The patient remained in perfect health until October, 1932, when without warning there suddenly developed upper abdominal cramping pain, fever, and deep jaundice

On the man's return to the clinic the jaundice was fully as deep as at the time of his previous visit There were no striking physical signs, except fullness of the upper part of the abdomen, and a questionably palpable left lobe of the liver The value for serum bilirubin varied from 16 to 21 mg in each 100 c c Traces of bile were found in the stools and duodenal content The galactose tolerance test gave a faintly positive result Roentgenologic examinations of the thorax and stomach did not disclose evidence of metastasis, but it was felt, nevertheless, that the malignant growth had extended into the liver Curiously enough the patient had no pruritus Because of the doubtful nature of the original lesion, exploration was made through a small incision November 17 The liver was found to be riddled with carcinomatous nodules Biopsy of one of these nodules disclosed adenocarcinoma, graded 3 Obstruction to the bile passages could not be demonstrated The patient is still under observation in the hospital but has had no return of pruritus

Comment on Cases I and II —These two cases represent the more intractable and severe type of pruritus associated with carcinoma of the head of the pancreas and with biliary obstruction In each instance all three types of palliative treatment

were employed with variable success, ergotamine tartrate was productive of the most relief In Case II there was remarkable freedom from pruritus following performance of cholecystgastrostomy This relieves the pruritus so uniformly in cases of this type that in many instances we feel that the operation is worth doing for this reason alone

Case III —A physician aged sixty seven years registered at the clinic January 4 1932 He gave a history of having had vague digestive disturbances for a long time but he had had no serious illness until six weeks prior to registration At that time he had been seized with sudden pain in the right upper quadrant of the abdomen for relief of which morphine had been required Four weeks later there had been a similar but much milder seizure following which generalized pruritus and later jaundice developed

On physical examination the man seemed to be in excellent general condition and had lost only about 15 pounds (about 7 kg) He was deeply jaundiced The heart and lungs were essentially normal. The abdomen was obese and difficult to examine. No abdominal tumor could be made out and the liver was barely palpable There were no other significant abnormalities. The urine contained large quantities of bile but was otherwise negative. The value for hemoglobin was 16 2 gm in each 100 c c leukocytes numbered 5 200 to 7 100 in each cubic millimeter of blood A serologic test for syphilis gave negative results Roentgenologic examinations of the thorax stomach and colon disclosed nothing of importance The value for serum bilirubin was 13 6 mg in each 100 c.c and the reaction was direct While the patient was in hospital under observation his stools were repeatedly negative for bile and on duodenal drainage only the faintest trace of bile could be recovered The value for serum bilirubin during this period of observation varied from 18 to 21 mg in each 100 c.c. It was felt that biliary obstruction was probably complete and that it was most likely due to neoplasm However the patient said that there had been many cases of catarrhal jaundice in his community and he preferred to wait a few days before surgical intervention was undertaken

During this interval an opportunity was afforded to try symptomatic treatment of the pruritus January 6 0 5 mg of ergotamine tartrate was given intramuscularly with complete relief for twenty-one hours, and the same dose was repeated on the following day with approximately the same results. January 9 repetition of this same dose gave complete relief for about ten hours. The onset of relief in this patient s case was sudden the itching often being considerably reduced within fifteen minutes after the injection had been given On the four following days pruritus was kept under complete control by the use of from 0 5 to 1 mg of ergotamine tartrate daily At exploration January 13 the gallbladder was found to be somewhat distended and the common bile duct dilated and tense. On further exploration the obstructing lesion was found to be a carcinoma of the common bile duct situated just above the ampulla of Vater Cholecystostomy was performed

the gallbladder being too necrotic to permit cholecystgastrostomy Following establishment of external biliary drainage, the pruritus was apparently almost entirely relieved

SUMMARY

It will be noted, from the cases presented and from the tables that no one form of treatment for pruritus of jaundiced patients is successful in each case and that the results may not be consistent even in the same case This phenomenon is difficult to explain, since little is known about the cause of pruritus under these conditions and still less about the mechanism by which relief is produced Calomel apparently does not always exert its cathartic effect in cases of jaundice, and can hardly be said to act as an eliminant The effect of sodium thiosulphate on pruritus is also unknown, but it has been used in various pruriginous types of dermatitis[5] with good effect It may possibly exert its effect directly on the skin, and act as a reducing agent on toxic products at this point It may at times be a very effective antipruritic agent in cases of jaundice, but its effects are not consistent in any large series of cases

Ergotamine tartrate has been more nearly uniformly effective in our experience It has been suggested by Lichtman that this substance exerts its effect by decreasing the irritability of the sympathetic nervous system Youmans and Trimble, however, have shown that small doses do not significantly affect the sympathetic mechanism of animals Lawrence has demonstrated that ergotamine tartrate may inhibit glycogenolysis in normal animals by affecting the sympathetic nerve supply of the liver He also has said that it diminishes the hyperglycemia from endogenous sources in cases of diabetes, and that it may also diminish the alimentary hyperglycemia in normal and diabetic subjects He expressed the belief that this is due chiefly to its effect on the motor activity of the upper part of the digestive tract Bauer and Wozasek have claimed that ergotamine tartrate diminishes galactosuria of normal persons and of subjects with hepatic disease, and that it may have some effect on hepatic function With so little known of its pharmacologic action and of its effect in hepatic disease, it would seem advisable to regard

it purely as an empiric remedy It appears to be the most valuable antipruritic agent for jaundiced patients which has as yet appeared, and has certainly added greatly to the comfort of patients under our observation We have given it orally in doses of 1 mg every three or four hours, which controls the itching effectively in the majority of cases The intramuscular route is preferable, however, when the itching is severe No systemic effects of any consequence have been noted in our series of jaundiced patients, however, the unpublished studies of Ceder raise the question of possible toxic effects in certain cases He has noted a very rapid and alarming rise in blood pressure, with headache, syncope, tachycardia, and threatened collapse in two cases following intramuscular injection of 0 5 mg of ergotamine tartrate The effects passed off within a few minutes, and apparently were not serious

For intractable pruritus which is not relieved by any of these three measures, establishment of a biliary fistula, or performance of cholecystgastrostomy, gives complete relief

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FOREIGN BODIES IN THE AIR AND FOOD PASSAGES REPORT BASED ON 334 CASES

PORTER P VINSON

In spite of warnings from the lecture platform and the press, introduction of foreign bodies into the esophagus and tracheobronchial tree persists as one of the tragedies of childhood Although removal of foreign bodies comprises less than 10 per cent of the work of the bronchoscopist, this is not due to decrease in the number of such accidents but rather to increase in the use of the bronchoscope as an aid to diagnosis of many pulmonary diseases It is the purpose of this report, based on 334 cases of this type, to present some of the data that are rarely obtained

The number of foreign bodies seen by a bronchoscopist will depend to a great extent on the density of population in his vicinity Foreign bodies are usually considered emergency problems, and patients are rushed to the nearest bronchoscopist for immediate attention It was of considerable interest to note that in this group of cases, thirty-one were local residents and 195 others were from Minnesota, Iowa, and Wisconsin

TYPES OF FOREIGN BODIES

Many types of foreign bodies were observed in this series but those most frequently encountered were nuts of various kinds, including peanuts Contrary to the experience of many observers, I have not found that peanuts present any greater problem than any other type of vegetable foreign body Meat and fish bones in the esophagus and bronchi were next in frequency Almost all chicken bones were of the type represented in Figure 227 The foreign bodies were as follows bones (meat and fish), forty-six cases, peanuts and shells, forty-one, pieces of metal, thirty-one, nails, tacks, screws and staples, together, twenty

nine, coins, twenty-four, safety pins, twenty-three, meat, twenty-one, corn or pop corn, nineteen, buttons, sixteen, straight pins and needles, together, fourteen, fruit pits, twelve, watermelon seeds, eight, pulmonary stones and teeth, seven each, nuts, other than peanuts, six, pieces of glass and seeds, four each, beans, three, and egg shell, oyster shell, pebbles, and carrots, two each There were also a shawl pin, a bead, an apple blossom, a piece of orange pulp, a disk used in the game of tiddley-winks, a snail shell, a doll's foot, a baby's pacifier, a piece of putty, a

Fig 227 —Type of chicken bone usually encountered in esophagus

toothpick, and a thorn The foreign body was in the esophagus in 135 cases, in the right bronchus in 102, in the left bronchus in fifty-six, in the trachea in twenty, in the pharynx in fourteen, in the larynx in six, and in a bronchus, but which one was not recorded, in one case The time of ingestion or inhalation of the foreign body, or the onset of symptoms in cases in which a foreign body was not suspected, varied from a few hours to thirty-eight years before endoscopy was performed In forty-three cases, the foreign body had been present for a few hours, in 144, from one to five days, in fifty-nine, from six to twenty-

one days, in forty six, from twenty two days to one year, and thirty three patients had harbored the foreign body for more than a year In nine cases, the duration of symptoms was not stated

The esophagus is particularly intolerant to the presence of a foreign body, especially of bones Even a metallic substance will soon produce acute esophagitis and this is induced much more rapidly by a bone with a portion of meat attached With the exception of three cases in which metallic foreign bodies had been present in the esophagus respectively for six months, ten months, and four years, the body had been in the esophagus a few hours or a few days Other features of the esophageal foreign bodies were that they always produced symptoms and were never overlooked except in cases in which patients had strictures of the esophagus Thirteen foreign bodies were removed from the esophagus of patients who had benign cicatricial strictures

As has been stated previously, foreign bodies in the esophagus are rarely overlooked, but such is not the case with foreign bodies in the bronchi In twelve cases, the presence of a foreign body in a bronchus was not suspected until bronchoscopy was done This fact emphasizes the necessity for bronchoscopic study in all cases of suppurative pulmonary disease, unless tuberculosis is known to be present.

AGE AND SEX

All bronchoscopists have had the experience that foreign bodies are more often found in the esophagus and respiratory tract of males than of females, and this was true in my cases One hundred seventy-seven patients were males and 157 females The ages are shown in Table 1 The number of patients less than five years of age, and the number less than ten years of age, as well as the number who were more than sixty years of age, were especially large Under-developed or dulled reflexes, and absence of teeth, very possibly account for such accidents in both the very young and the very old In one instance only was a nut kernel present in the respiratory tract of a child more than five years of age. In this case the child was seven

TABLE 1

AGES OF PATIENTS WITH FOREIGN BODIES IN THE ESOPHAGUS OR RESPIRATORY PASSAGES*

Age, years	Number of foreign bodies
1 to 5	165
6 to 10	41
11 to 15	11
16 to 20	11
21 to 25	14
26 to 30	11
31 to 35	10
36 to 40	6
41 to 45	13
46 to 50	13
51 to 55	7
56 to 60	7
More than 60	19

* Oldest, eighty years, youngest, two months Age of six patients not recorded

years old In view of this, one can feel reasonably safe in giving nuts to children who are six years of age or older, if they eat carefully The objection to this conclusion is that nuts are likely to be eaten between meals, when children are playing, and when they are under little supervision

ANESTHESIA

There has always been considerable controversy as to the advisability of using general anesthesia during esophagoscopy and bronchoscopy for foreign bodies Ether anesthesia was employed in 116 of my cases I am now of the opinion, however, that local anesthesia, or none, is preferable in cases in which foreign bodies are in the respiratory tract, but ether anesthesia should be employed in cases in which large foreign bodies are in the esophagus of adults, and in all cases in which foreign bodies are in the esophagus of children I have never seen any untoward results from using ether anesthesia in these cases, and in most instances esophageal trauma is reduced to a minimum There is a definite risk associated with general anesthesia of children who have foreign bodies in the respiratory tract, and these patients are given a hypodermic injection of $\frac{1}{4}$ to $\frac{1}{2}$ grain (0 016

to 0 032 gm) of codeine sulphate and 7 to 10 grains (0 45 to 0 65 gm) of chloral hydrate in a small amount of warm milk, by rectum, about a half hour to three-quarters of an hour before the bronchoscopic examination is performed For adults, a preliminary injection of $\frac{1}{6}$ to $\frac{1}{4}$ grain (0 01 to 0 016 gm) of morphine sulphate may be given a half hour before examination, with the application of 20 per cent solution of cocaine hydrochloride to the pyriform fossa and larynx, and instillation of 2 c c of the same drug, in 5 per cent solution, into the trachea

POSTOPERATIVE CARE

There is rarely any reaction following esophagoscopy for diagnosis or for removal of a foreign body, but laryngeal edema may develop in children less than seven years of age after bronchoscopy, and this may become so pronounced as to necessitate tracheotomy It is impossible to anticipate the occurrence of edema of the larynx. Among children who have a small laryngeal aperture, edema may not occur even after prolonged instrumentation, whereas in an older child, with a large opening, it may develop within a few hours after a short examination, entailing a minimal amount of trauma

Inhalation of steam after bronchoscopy seems to increase traumatic laryngeal edema and I have discontinued its use

Administration of oxygen in a tent or chamber, following bronchoscopic examination of children five years of age or less undoubtedly has been of value in preventing laryngeal edema or in obviating the necessity for tracheotomy Fifty seven patients in this age group were not given oxygen after bronchoscopy, and tracheotomy was necessary in twenty cases, whereas of forty patients who were given oxygen only nine required tracheotomy At present, all of my patients who are less than five years of age are given oxygen immediately following bronchoscopic examination

It is very likely that tracheotomy was performed on patients who would have survived without the operation, but it is far better to open the trachea as soon as breathing becomes definitely obstructed, when there is very little surgical mortality,

than to wait until marked symptoms of obstruction have developed and the operation is done as an emergency measure

Results of treatment—In 298 cases, removal of the foreign body was followed by immediate benefit and in most of them by complete recovery In a few cases, in which a foreign body had been in the lung for many years, chronic bronchiectasis had developed and the patients continued to have chronic cough, with expectoration of varying amounts of sputum Fifteen patients declined examination In five cases the foreign body was not removed One of these was an ordinary pin in a terminal bronchus and the smallest forceps available could not be introduced into the bronchus far enough to engage the foreign body Two patients had foreign bodies beyond strictures in the bronchus One refused further examination after the stricture had been dilated, but the other had a second bronchoscopic examination later at her home, with the removal of the foreign body This proved to be a piece of bone In one case a metallic foreign body was presumably in the bronchus, although there was no history of aspiration and pulmonary symptoms were absent Bronchoscopy under fluoroscopic guidance, was done but the foreign body could not be found The fifth failure was in the case of a child who had had a tack in the bronchus for seven months Many attempts were made to grasp the foreign body at bronchoscopy but external operation was required to remove it

A foreign body in the esophagus or tracheobronchial tree always constitutes a serious condition, and the younger the patient, the greater the chance of a fatal termination

Death resulted in sixteen of my cases, and analysis of the causes of death may be of value Ten deaths followed removal or attempts at removal of foreign bodies from the respiratory tract In two of these cases, previous instrumentation elsewhere had been followed by perforation of the trachea and bronchus In one case, surgical collapse of the lung for suppurative disease following prolonged sojourn of a pulmonary stone that had not been identified at bronchoscopy resulted fatally In a case somewhat similar, a portion of a pulmonary

stone had been removed at bronchoscopy, but later multilocular empyema, with terminal bronchopneumonia, developed At the beginning of general anesthesia for examination of a child with a kernel of corn in a bronchus the foreign body was dislodged, became impacted in the trachea, and caused death before it could be removed A child died from exhaustion in the course of emergency bronchoscopy for removal from the trachea of a kernel of corn The patient was in a desperate con

Fig 228 —Tie-clasp impacted in left main bronchus.

dition at the time of admission to hospital, and it seemed that bronchoscopy offered a greater chance of recovery than tracheotomy Two children had such large foreign bodies in the trachea that efforts at removal resulted in fatal trauma One of these bodies was a tie clasp which was impacted partly in the left bronchus (Fig 228), and the other was the foot of a doll measuring 1 2 by 5 cm Two children died following tracheotomy after the foreign body had been removed Six deaths followed impaction of foreign bodies in the esophagus One patient had

had a large peach stone impacted in the lower part of the esophagus for one month, and efforts to remove it were followed by mediastinitis and death In another case, the foreign body, an open safety pin, had caused ulceration through the esophagus into the posterior mediastinum, and an effort at surgical removal six weeks later resulted fatally (Fig 229) In another case, of similar type, a metallic foreign body had ulcerated into the larynx, and surgical removal was followed by death a week

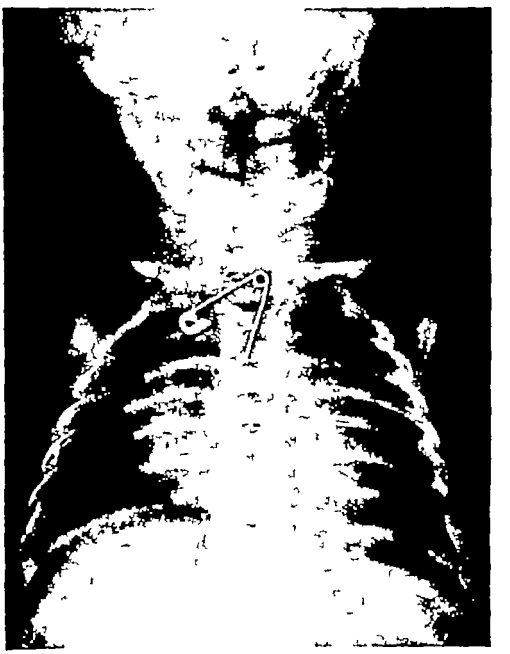

Fig 229 —Open safety pin entirely outside the lumen of the esophagus

later Fatal perforation of the esophagus occurred in one case in which a coin had been present for four days, and the same accident occurred in another case in which the point of an open safety pin was accidentally pushed through the wall of the organ in the course of removal Another death occurred suddenly on introduction of the esophagoscope, the patient was a child with an open safety pin in the esophagus The cause of death could not be determined at postmortem examination

THE ASSOCIATION OF DISEASES REPORT OF TWO UNUSUAL GASTRO-INTESTINAL CASES

DWIGHT L. WILBUR

One of the most interesting chapters in medicine is that of the association or coincidence of diseases affecting the same person, and yet very little is known or thought about this subject. Not only is it of interest because of the constitutional, etiologic and pathologic physiologic aspects of the subject, but it is of great importance in diagnosis and in treatment, as will be pointed out. The general concepts of disease and the known facts regarding the resistance of the body to disease are sufficiently known and too detailed to be considered fully in this paper, although they form the foundation on which knowledge of the significance and etiology of association of various diseases will eventually depend.

Most physicians' ideas concerning the coincidence of diseases are based on clinical impressions and studies of relatively small series of cases, consequently what is now considered to be known about this subject may eventually be found not to agree with facts. Statistics concerning the incidence of certain diseases are generally made on a selected group of the population, such as those seeking hospital care, insurance disability, and the like. It is difficult to obtain statistically satisfactory and uniform conditions to study the coincidence and association of distinct diseases. When such information is available there will come into existence a tremendous body of knowledge with regard to the influence of disease processes on man.

It has long been taught that an attempt should be made to explain the symptoms presented by a patient on the basis of a single diagnosis. This is an excellent principle, provocative of thought, and leading more often than not to a correct diagnosis

It, however, fails in cases in which more than one disease is actually present This is particularly true in relation to problems of diagnosis and treatment in gastro-intestinal disturbances In such conditions decision must be made first, as to whether the disturbance is functional or organic, and second, as to whether more than one disease process is present in a given case Failure in treatment may depend on an associated but unrecognized lesion Unfortunately, figures for such association are, as a rule, unreliable But that the recognition of such an association is desirable is indicated by the studies of Rivers and Hartman, who found in a study of 1,075 surgical cases in which a preoperative diagnosis of duodenal ulcer only had been made, that 7 4 per cent revealed associated subacute appendicitis, 3 6 per cent associated cholecystitis, 3 6 per cent associated gastric ulcer, and 3 per cent miscellaneous lesions In a similar study of 879 cases in which the diagnosis before operation was cholecystitis or cholelithiasis only, the most significant of the complications discovered during the operation was carcinoma involving the gallbladder, bile ducts or liver In an attempt to establish statistically a clinical impression that carcinoma of the stomach rarely is associated with an active duodenal ulcer, Rivers and I reviewed the records of such cases in The Mayo Clinic Unfortunately, it was not possible to prove the point that a person with active duodenal ulcer and high gastric acidity is less subject to the development of gastric carcinoma than is a normal person, but the few cases in which the lesions were associated in our series strongly suggested that this was the case

In the course of these studies the following two histories were encountered, in which the association of such an unusual number and variety of gastro-intestinal lesions in both seemed worthy of note, although the significance of this association cannot as yet be estimated In the first case the following gastro-intestinal lesions were present esophageal epithelioma with clinical symptoms of irritation, carcinoma of the stomach with hepatic metastasis, multiple duodenal ulcers with obstruction, chronic cholecystitis with cholelithiasis, severe hepatic injury, and acute hemorrhagic pancreatitis In the second case the

lesions present were widespread gastric polyposis, duodenal ulcer with slight obstruction, and carcinoma of the islands of Langerhans with clinical symptoms of hyperinsulinism It is also interesting to note that both of these patients were comparatively young

REPORT OF CASES

Case L—A woman aged forty three years registered at the clinic January 28 1931 because of pain in the epigastrium of three weeks duration She had been seen previously on several occasions during pregnancy and in 1915 thyroidectomy for adenoma of the right lobe had been performed The distress complained of at this time followed closely the beginning of pregnancy estimated to be of two months duration at the time of admission There was pain and a feeling of pressure in the epigastrium worse after eating and at night. Subsequently pain developed between the shoulders coming through to the epigastrium occurring in attacks lasting from half an hour to five hours.

Examination revealed that the patient was pregnant and also that there was tenderness in the region of the gallbladder A roentgenologic study of the gallbladder revealed that the organ was not functioning and that many stones were present Therefore February 21 1931 cholecystectomy was performed for chronic cholecystitis with stones The pancreas was reported to be apparently normal at this time Convalescence was uneventful except for a slight respiratory infection

The patient returned March 18 1931 because of vomiting and pain in the right shoulder and infrascapular region similar to that which had occurred before operation but which was more severe and required opiates for relief There was evidence of toxemia of pregnancy Jaundice did not develop The test of hepatic function by the dye method gave evidence of retention graded 4 but this gradually cleared up with treatment and later the retention was only of grade 2 Hiccough occasional dysphagia and vomiting persisted for some time and was refractory to treatment Roentgenologic study of the stomach and duodenum April 21 1931 revealed a duodenal ulcer with obstruction. Hypertrophic arthritis of the thoracic portion of the spine was also noted. A history of previous symptoms of ulcer could not be obtained The condition of the patient improved considerably when an ulcer regimen was instituted, but complete relief was not obtained The symptoms were not distinctly those of duodenal ulcer

The condition of the patient was somewhat improved until June 1931 when she returned to the hospital because of increasing restlessness and weakness at one time she had fainted The gastric symptoms had continued and could not be satisfactorily explained Loss of weight anemia and occasional vomiting were present, and the epigastric and infrascapular pain, with burning in the esophagus recurred Considerable diarrhea was present. The pain was sufficient to keep the patient awake at night Early in July 1931, she had several attacks of vertigo and syncope. After one such attack, July 7 labor began and an infant was delivered spontaneously July 8 Twelve

hours after delivery the patient went into profound shock The blood pressure in millimeters of mercury was 80 systolic and 40 diastolic She revived following intravenous injection of fluids, but went into shock again several times, becoming practically pulseless Despite intravenous injections of acacia and saline solutions, and transfusions of blood the patient gradually lapsed into coma with rising temperature and falling blood pressure, and death occurred July 12, 1931

At necropsy, examination of the gastro intestinal tract revealed changes in the esophagus, stomach, liver, duodenum, and pancreas The esophagus presented epitheliosis consisting of marked thickening of the epithelial layer On the greater curvature of the stomach 8 cm from the pylorus there was an indurated ulceration 12 by 6 mm , with raised pearly margins The peritoneal surface overlying this was white and indurated Microscopic examination of this tissue disclosed adenocarcinoma In the duodenum, on the posterior wall, was a deep perforated ulcer 2 cm in diameter, and a similar ulcer 13 mm in diameter was present on the anterior duodenal wall 2 cm beyond the pylorus, which perforated onto the head of the pancreas The liver weighed 2,700 gm and scattered throughout it were five carcinomatous nodules, varying in size from 3 to 6 cm Microscopic study of the liver revealed some atrophy in the central portions of the lobules, and with the use of the fat stain a moderate amount of finely dispersed fat was observed in the hepatic cells The pancreas weighed 125 gm It was firm, indurated, grayish-black, with mottled red and white areas There was a good deal of fatty necrosis in the surrounding fat and also in the mesenteric fat

Several factors are worthy of comment regarding this remarkable case The occurrence of a serious disease in each of the organs of the upper part of the gastro-intestinal tract is very unusual, and such an occurrence in a woman, aged forty-three years, who otherwise apparently had always been in good general health, seems to be more than mere coincidence However, there were no facts to offer in substantiation of this point of view, especially because of the diversity of the lesions and because of the widely differing etiologic factors generally supposed to be responsible for them

The condition of the esophagus may have been the result of fairly constant regurgitating and vomiting Esophageal irritation is not uncommon under such circumstances The carcinoma of the stomach was unsuspected clinically, and as can be judged from its small size and position it could hardly be expected to have produced recognizable symptoms It consisted of a small ulcerated plaque, approximately 1 cm in diameter, on the greater curvature of the stomach, and attention was called to it in par-

ucular by the presence of several metastatic areas in the liver Carcinoma of the stomach rarely begins on the greater curvature The duodenal ulcer with pyloric obstruction was found on roentgenologic examination of the stomach and duodenum Even with this in mind, careful questioning of the patient failed to reveal any symptoms suggestive of duodenal ulcer prior to the present illness, and at an abdominal operation two months previously it had not been noted The clinical evidence of its occurrence during the present examination was fairly distinct, for the symptoms complained of were in part suggestive of duodenal ulcer although careful medical treatment of ulcer failed to relieve the symptoms more than partially The occurrence of obstruction is the only point suggesting that the lesion was chronic. The history of cholecystitis with stones was of short duration, and this may have been accounted for by aggravation incident to the pregnancy The presence of hepatic disease was indicated by the occurrence of retention of dye, graded 4, in the course of the test of hepatic function, clinically by the presence of toxemia of pregnancy, and anatomically by hypertrophy, fatty change and atrophy of the central areas of the hepatic lobule The liver was the seat of carcinomatous metastasis, but the growths were not large enough to have accounted for all of the hepatic symptoms, nor for the retention of dye It is difficult to know how long the pancreatitis had existed The presence of so much severe pain in the back and the occurrence of diarrhea suggest that a pancreatic lesion may have been present before the development of shock, which was obviously precipitated by the acute hemorrhagic process in the pancreatic tissues

Case II.—A man aged thirty two years registered at the clinic August 4 1931 because of periods of weakness The family history and past medical history were essentially negative except for typhoid pneumonia in 1915 In April 1930 (sixteen months prior to registration) nausea and slight abdominal pain developed with relief after taking food or after vomiting The pain and nausea occurred several hours after meals and persisted over a period of two weeks. September 1930 the patient slept heavily and later than usual and reported that he was aroused with difficulty under such circumstances he stated he was semistuporous confused and disoriented

Easy fatigability and loss of weight were associated with these symptoms In October, 1930, because of these symptoms, the patient was studied carefully at another hospital, and a diagnosis of hypoglycemia was made Since then he had used excessive amounts of sweets immediately before, during, and after meals, and found that he got along well in this way Occasionally, however, when he forgot to take sugar, confusion, twitching of the hands, and stiffness of the right leg, subsequently developed, from which he obtained prompt relief by taking orange juice or an enema containing glucose Consciousness was not lost during these attacks

In May, 1931, gastro-intestinal symptoms similar to those that occurred in April, 1930, were present for a few days but they disappeared rapidly following dietary care

Physical examination was essentially negative except for loss of 15 pounds (6 8 kg) The blood pressure in millimeters of mercury was 116 systolic and 76 diastolic Laboratory studies made of the urine, and of morphologic features of the blood gave normal results Analysis of gastric content revealed free acidity of 48, and total acidity of 60, 40 c c of normal filtrate was obtained Flocculation tests of the blood for syphilis gave negative results The basal metabolic rate was +10 and +2 per cent on two occasions Roentgenologic examinations of the stomach and duodenum revealed a duodenal ulcer, with slight obstruction and extensive polyposis of the stomach Studies of the chemical constituents of the blood revealed a concentration of urea of 20 mg for each 100 c.c , and the sugar varied between 0 04 and 0 09 mg for each 100 c c The dye test of hepatic function gave no evidence of retention Results of a glucose tolerance test were reported as follows

	Blood sugar, mg	Urine volume c.c.	Urine, sugar
Before	0 04	25	0
½ hour	0 10	12	0
2 hours	0 06	0	
3 hours	0 04	49	0

A diagnosis of hyperinsulinism was made

August 24, 1931, at an exploratory operation, the stomach was found to be large and the site of diffuse polyposis The duodenum presented a fairly active ulcer, producing some obstruction On the anterior surface of the pancreas, at the juncture of the body and tail, was found a definite tumor, about 1 5 cm in diameter, and almost completely surrounded by pancreatic tissue. At the upper border of the pancreas, about 5 cm above this, was another tumor about 2 cm in diameter joined to a lymph node The tumors were excised and the pancreas was sutured

Pathologists reported that the tissue was composed of carcinoma graded 1 in adenomas of the islands of Langerhans

The patient recovered promptly, although he had a good deal of gastric distress which yielded fairly well to a medical regimen for ulcer

September 28, 1931, the pancreas was irradiated and October 2 the patient was dismissed from our care, feeling well A year later he reported by letter that he was in perfect health

In this case, the occurrence of hyperinsulinism dependent on adenocarcinoma of the tissue of the islands of Langerhans in the pancreas is worthy of note, especially since it occurred in a young man. The presence of the associated duodenal ulcer with slight obstruction and extensive gastric polyposis was apparently coincidental It will be interesting to note if in subsequent years there is further development of disease of the upper part of the gastro-intestinal tract

GENERAL COMMENT

If in either of these cases the patient had been old, in the period in which degenerative diseases chiefly occur and in which resistance to disease is lowered, the association of so many diseases might not have been surprising

So few facts are known regarding the association of diseases that the following consideration is concerned chiefly with problems which have interesting and practical aspects in regard to this association

Etiologic consideration—Because of the wide variety of physical and chemical agents which produce disease, and the variability of form in which they can lower the resistance of the body, it is not surprising that diseases are often associated A physician's difficulty is chiefly in recognizing the significance of such an association The importance of the constitution of the individual in this regard is expressed in the words of Peterson "We are justified in drawing the conclusion that fundamental differences in the hormone and chemical constitution of the individual find expression not only in pathological but in physiological and psychic reactions of the utmost importance"

Among the factors that lower resistance of the body is the presence of a chronic disease It is well known that many patients with chronic diseases die of acute infections, and it is presumably the lowered resistance produced by the chronic disease which leads to the associated acute condition Death certificates call for the recognition of such an association, and the classification of the diseases present as primary and secondary, or as contributing Occasionally these may be the result

of a single cause, such as mitral endocarditis with cardiac failure, or they may be entirely separate, as in the cases of cirrhosis of the liver terminated by an infectious disease, such as bronchopneumonia

Any factor such as an epidemic which tends to cause disease of a large number of persons simultaneously is certain to lead to an association of diseases, since many persons affected by the epidemic already harbor diseases of other types Similar factors are encountered among those living under identical environmental conditions or exposed to similar dietary deficiency or intoxication, as for example, food poisoning

Physical and mental diseases are frequently associated, and they may or may not be etiologically associated In this connection it may not always be clear whether the conditions present have much etiologic relationship, whether the physical or mental condition is symptomatic or an actual disease entity Physical disease may bring to light mental disease previously latent, and the reverse also holds true

Now that diseases are considered particularly from their etiologic and pathologic aspects rather than on the basis of symptoms, many conditions previously considered separately have been found to be related, and are known now as distinct diseases, syndromes or polyglandular disturbances Conditions now considered independent although often associated may eventually be found to be due to a single process An excellent example is afforded by the achlorhydria, anemia and changes in the nervous system noted in pernicious anemia The occurrence of any one of these three conditions alone might have been considered as evidence of a distinct disease, or together as an association of diseases, but advancement of knowledge has demonstrated that they are fundamentally related

Two other factors must be considered in the coincidental occurrence of diseases These are symbiosis and syntopie Symbiosis is a well-established biologic fact, but little thought seems to have been given to the possibility that symbiosis may be of importance in the relationship of etiologic factors of disease and the host The subject requires further study "Syn-

topic of diseases" is a term applied by Pfaundler and Scht to the mutual attraction and relations between morbid conditions, simultaneously or in sequence These investigators worked out a formula for the determination of such syntopic and found, for instance, syntopic between cystitis and hemorrhagic diathesis, and between endocrine derangement and inherited syphilis in a group of 1,151 children in Münich

Diagnostic considerations —From the diagnostic standpoint the association of diseases is of significance It has already been stated that it is current medical practice to try to correlate all the symptoms of a patient on the basis of a single diagnosis The association of diseases makes this more difficult, especially if the disease processes influence the same or adjacent organs, and not infrequently confusion is the result This is particularly true of those diseases which may manifest themselves in different ways, or which may affect a variety of organs and thereby simulate other conditions, syphilis, tuberculosis, and malignant tumors fall into this group For example, in considering a patient with syphilis, manifestations of disease in the nervous system, heart or stomach may be due to syphilitic involvement of these organs or to the nerve pathways connected with them, but they may also be due to unrecognized associated disease, such as tumor of the brain, rheumatic endocarditis, or gastric carcinoma The reverse holds true also, and occasionally in a case of unrecognized tabetic gastric crisis, exploration is done for a suspected acute abdominal condition Similarly, the occurrence of metastatic lesions in cases of malignant neoplasm may lead to confusion in diagnosis The presence of referred pain may lead to error or difficulty of diagnosis The simultaneous occurrence of herpes zoster affecting the upper abdominal region on the right side, and an attack of gallbladder colic make diagnosis extremely difficult Referred pain in the neck in lesions affecting the diaphragm, or pain in the knee in lesions affecting the obturator nerve, similarly may make diagnosis difficult, especially if associated disease is present in the region of referred pain

The classifying of a symptom as a disease should not lead

to diagnostic difficulty in the recognition of associated disease The occurrence of anemia with tuberculosis, of delirium and delusions in states of fever, or of headache with gastro-intestinal stasis must not be considered as due to the association of distinct disease processes responsible for the anemia, delusions or headache, since they are more likely symptomatic, yet it should be remembered that distinct diseases may be responsible for the simultaneous occurrence of these symptoms

One of the difficulties in cases of mental or nervous disturbance is the estimation of the significance of symptoms related to various organs It not infrequently happens that the psychoneurotic patient with abdominal pain fails to obtain relief because associated organic disease is not found and corrected On the other hand, symptoms regarded as psychoneurotic or hysterical displayed by a patient who is acting strangely may eventually be discovered to be caused by a lesion of the frontal lobe of the brain The occurrence of an independent organic disease may cause the patient to break down with anxiety neurosis, psychoneurosis or dementia præcox, previously unsuspected

Certain diseases are apparently rarely associated Hitzrot reported that the coincidence of diabetes and pernicious anemia is extremely rare, and he found only six cases (to which he added one case) reported in the literature up to 1929 Subsequently Root (1931) reported a total of forty-eight cases (including those in the literature and his own cases) After studying a series of 628 cases of pernicious anemia, Giffin and Bowler remarked on the absence of active tuberculosis in association with this disease as a notable feature On the other hand, statistical evidence indicates that there is a positive frequency relation between hyperthyroidism and carcinoma of the stomach not only in the United States but also in Switzerland Certain diseases are regarded as antagonistic, for example, malaria and carcinoma, and it has been suggested that the uncommon occurrence of carcinoma in tropical countries is due to the prevalence of malaria

It is of interest to note the incidence of associated multiple growths in cases of malignant neoplasms Owen placed this

incidence at 4 7 per cent Hurt and Broders, in a recent study of more than 2,000 cases in which microscopic diagnosis of malig nant neoplasms was made, found evidence of independent mul tiple malignant neoplasms in 3 34 per cent They stated that, if those cases in which clinical diagnosis has been made also were added to this series, the percentage of multiple malignant neoplasms would have approached or exceeded that of Owen

Therapeutic considerations—In the treatment of disease the physician is concerned not only with the nature of the disease, but also with the stage to which it has advanced He is on the alert for complications and sequelæ and he should be mindful of intercurrent or associated disease for these may significantly alter his therapeutic measures and the success of his efforts

From the standpoint of the patient and physician, the simul taneous association of several disease processes may be very important, because the disease processes may have beneficial or detrimental effects on one another It is equally possible that they will be without influence on one another

It is well known that acute infections have a detrimental influence on chronic diseases This is particularly noted in diabetes, Addison's disease and arthritis which may become severe during the course of an acute respiratory or other infec tion Under such circumstances the chronic disease may be very refractory to treatment

On the other hand, the simultaneous occurrence of certain infectious diseases, particularly those accompanied by much fever, may have a beneficial effect on a chronic disease This principle has been used in treatment of such conditions as paresis by inoculation with malaria, and in arthritis, iritis, and other chronic inflammatory diseases by inoculation with typhoid vaccine, and other agents producing febrile reaction and pro-tein shock.

It seems probable that many coincident diseases will have no influence on each other The occurrence of syphilis with many other conditions, such as carcinoma of the stomach or leiomyoma of the uterus, would apparently be without mutual effect many other examples could be quoted

It should be reemphasized that the therapeutic problems raised by the association of diseases may be great, and treatment may become very difficult under such circumstances If a therapeutic regimen is carried out by the patient and is a failure, the physician should be led to suspect first, an erroneous diagnosis, and second, the presence of an unsuspected complication or associated disease

Statistical consideration —Statistical evidence will eventually disclose many of the unknown facts regarding the significance of the association of diseases At present, facts regarding the incidence of a single disease in the average population are difficult to obtain Most figures are based on selected populations, or are unsuitable for careful statistical analysis for other reasons This is particularly true of morbidity statistics Every effort should be made by statisticians to see that the figures they present are as reliable as possible, but this should not at the same time limit publication to material which statistically is ideal Under such conditions progress is too slow The presentation of carefully compiled statistical material, under reasonably satisfactory conditions, and with a statement as to the conditions of collection of the material, will not only be a distinct advance, but will be stimulating to others and to the advancement of knowledge It will give much information concerning the significance of the association of diseases

SUMMARY

Two case histories illustrating an unusual association of gastro-intestinal disease have been presented In the first case esophageal epitheliosis with clinical symptoms, carcinoma of the stomach with hepatic metastasis, multiple duodenal ulcers with obstruction, chronic cholecystitis with cholelithiasis, severe hepatic injury and acute hemorrhagic pancreatitis were present In the second case widespread gastric polyposis, duodenal ulcer with slight obstruction and carcinoma of the islands of Langerhans with clinical symptoms of hyperinsulinism were present

Some of the etiologic, diagnostic, therapeutic, and statistical considerations of the association of diseases are considered

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THE PROGRESSION OF MYOCARDIAL DISEASE AS RECORDED BY SERIAL ELECTROCARDIOGRAMS

FREDRICK A WILLIUS

Careful observation of patients with myocardial disease over a period of months or years frequently enables the clinician to record interesting changes in the function and structure of the heart. Electrocardiographic study at intervals permits a permanent serial record of intricate changes as they occur, changes that for the most part would otherwise remain unidentified These graphic alterations are frequently very important prognostic guides that may influence the treatment to a considerable degree

It is well recognized that distinctive electrocardiographic alterations occur following cardiac infarction, which involve the form and direction of the T waves[4, 6] and the R-T segments [1, 3, 5] I shall not attempt to consider these abnormalities in detail, since such data may be found in published works on the subject I emphasize the fact that cases of infarct are excluded because the electrocardiographic changes forming the basis of this report are not the result of coronary thrombosis with resulting myocardial infarction, but represent more or less insidious changes resulting either from gradual occlusive arterial disease or from progressive cardiac hypertrophy, or possibly the concomitant effect of both processes I have not considered cases of auricular fibrillation or auricular flutter, since their incidence in heart disease is so general and the significance of their presence varies so greatly in individual cases

PROGRESSION FROM DELAYED A-V CONDUCTION TO COMPLETE HEART BLOCK

Case I.—A man aged seventy two years presented himself for examination November 26 1929 because of dyspnea and palpitation occurring with undue effort. These symptoms had been present for six years and were grad

ually becoming more pronounced He had had pneumonia at the age of fourteen, occasional attacks of tonsillitis, and an acute febrile illness a year before admission that was said to be influenza

Examination revealed moderate sclerosis of the peripheral arteries The heart was not enlarged A rough, blowing systolic murmur was best heard over the aortic area and the heart sounds were rather distant The systolic blood pressure was 182 and the diastolic pressure 100 in millimeters of mercury Urinalysis revealed only a faint trace of albumin The Wassermann reaction of the blood was negative The electrocardiogram (Fig 230, A) revealed delayed A-V conduction, the P-R interval measuring 0 25 second, which was not abolished by the administration of atropine hypodermically

A diagnosis was made of arteriosclerotic disease of the heart with delayed A-V conduction, and moderate essential hypertension Treatment for the cardiac condition was instituted and the patient was advised to return for examination within a year

The patient returned ten months later (September 23, 1930) His general condition was not unlike that disclosed by the previous examination However, during the previous three months slight upper retrosternal distress occurred with effort, or following the ingestion of an unusually heavy meal

The results of general examination were similar to those of the previous year with the exception of cardiac enlargement The total transverse diameter of the cardiac shadow in the teleoroentgenogram was 18 5 cm The blood pressure was 152 systolic and 78 diastolic Examination of the urine and of the fundus of the eyes gave negative results The electrocardiogram (Fig 230, B) showed the delayed A-V conduction to have increased, the P-R interval being 0 28 second

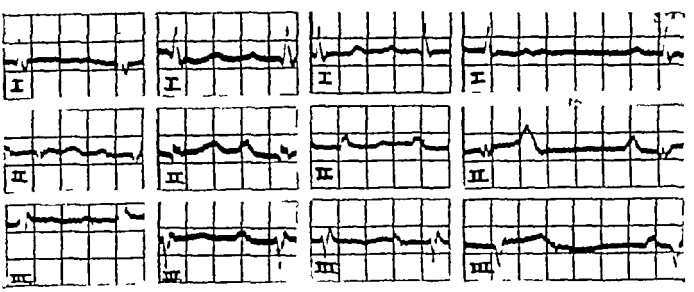


Fig 230—Successive electrocardiograms A, November 26, 1929, delayed A-V conduction, the P-R interval measures 0 25 second B, September 23, 1930, the conduction time has increased, P-R interval, 0 28 second C, January 17, 1931, P-R interval is still 0 28 second D, April 4, 1932, complete heart block, the ventricular rate was 46 and the auricular rate 79 beats each minute

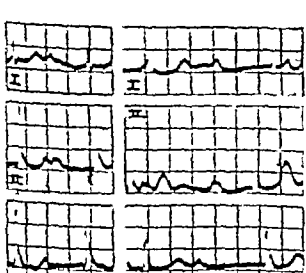
The patient was again examined four months later (January 17, 1931) at which time he had marked icterus, the result of calculus in the common bile duct This was preceded by a typical attack of cholecystitis He improved

while under observation and the icterus completely subsided thus deferring operation was justifiable The cardiac status appeared unchanged The systolic blood pressure was 145 and the diastolic pressure 75 The electrocardiogram (Fig 230 C) was similar to the preceding one the P R interval being 0.28 second.

Sixteen months later (April 4 1932) no new complaints were apparent and the patient felt that he was getting along satisfactorily The condition of the heart was not particularly different except that the rate was very slow (36 beats each minute) There had been no syncopal or convulsive seizures The systolic blood pressure was 146 and the diastolic pressure 74 The electrocardiogram (Fig 230 D) revealed the presence of complete heart block, the ventricular rate was 46 and the auricular rate 79 beats each minute.

The records in this case cover approximately two and a half years during which time a slight delay in A V conduction was found to increase, ultimately progressing to complete heart block The inference was progressive interference in the conductivity of the bundle of His resulting from obliterative arterial disease.

Case II.—A man aged forty three years was examined August 8 1929, because of epigastric pain Records of other illnesses except occasional



A B

Fig 231.—Successive electrocardiograms A August 8, 1929 marked delay in A-V conduction the P R interval is 0.36 second B Seven months later complete heart block the ventricular rate was 53 and the auricular rate 79 beats each minute.

attacks of tonsillitis were not elicited Eight months before examination he had experienced pain in the right lower abdominal quadrant which persisted for four days A similar but shorter attack occurred one month before

Four and a half months prior to examination he was suddenly seized with severe pain in the epigastrium associated with a sense of faintness, momentary syncope with rather marked slowing of the heart soon followed by rapid and forceful heart action These symptoms again occurred a week later

The patient did not appear to be acutely ill The heart did not appear to be enlarged, and the roentgenogram contained the shadows of a normal heart A faint blowing systolic murmur was audible at the cardiac apex and the first sound in this area was accentuated Systolic blood pressure was 136 and the diastolic pressure 90 The electrocardiogram (Fig 231, A) revealed marked delay in A-V conduction, the P-R interval being 0 36 second, uninfluenced by the administration of atropine hypodermically

A diagnosis was made of recurrent appendicitis, focal myocarditis (bundle of His) with delayed A-V conduction The patient was advised to restrict his activities as owing to the cardiac condition operation was deferred, and to return in a few months for examination

The patient reappeared seven months later, complaining of dyspnea occurring with undue effort and stated that his heart had been beating very slowly No further acute abdominal attacks had been experienced The heart appeared to be slightly enlarged to the left, the area of dulness extending 11 5 cm beyond the midsternal line The murmurs heard on the previous examination were distinctly louder The electrocardiogram (Fig 231, B) revealed the presence of complete heart block, the ventricular rate was 53 and the auricular rate 96 beats each minute

This case is similar to the preceding one except that the time interval is considerably less, only seven months elapsing between examinations Although positive proof is lacking owing to the patient's survival, an infectious lesion involving the bundle of His is the most plausible explanation of the events transpiring in this case

DEVELOPMENT OF T-WAVE NEGATIVITY

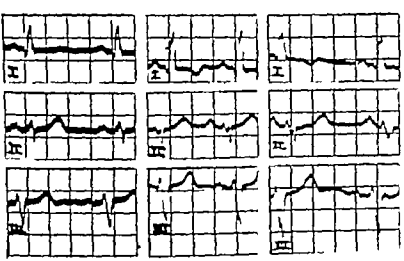
Case III —A man, aged fifty seven years, presented himself for examination December 12, 1927, because of dyspnea occurring on undue effort This complaint had been present in some degree for ten years He also complained of intermittent periods of irritability of the bladder and pus had been discovered in the urine from time to time. A conservative prostatectomy had been performed elsewhere two years previously He had suffered from recurrent bronchitis for several years

Examination revealed that the heart was not enlarged as evidenced by the teleoroentgenogram No auscultatory abnormalities were observed The blood pressure was 160 systolic and 92 diastolic Many pus cells were present in the urine Urologic study revealed the presence of chronic pyelonephritis Other special laboratory studies including the Wassermann reaction gave negative results The electrocardiogram (Fig 232, A) was essentially negative

A diagnosis was made of mild essential hypertension chronic pyelonephritis and recurrent bronchitis

The patient returned three years and nine months later complaining of more marked dyspnea on undue effort The bronchitis was still troublesome The heart was considerably enlarged the teleoroentgenogram showing the total transverse diameter to be 18 cm there was calcification of the arch of the aorta The rhythm was regular and murmurs were not audible. The systolic blood pressure was 122 and the diastolic pressure 80 The urine still contained numerous pus cells Studies of the blood gave negative results The electrocardiogram (Fig 232 B) showed negativity of the T wave in lead I Slurring and slight notching of the QRS complexes in leads I and III were evident but the base width of these complexes did not exceed 0 12 second

The patient was again examined four months later (January 22 1932) at which time the dyspnea had increased periodic episodes occurred ushered



A B C

Fig 232 —Successive electrocardiograms A December 12 192, an essentially normal record B Nine months later T wave negativity in lead I C, Four months still later In addition to the T wave negativity incomplete bundle-branch block.

in by chilly sensations fever and drowsiness and the cough and expectoration had increased The objective cardiac condition was apparently unaltered A moderate degree of pyuria was still present but at this time a roentgenogram of the thorax revealed the presence of a triangular shadow of increased density at the base of the right bronchus posteriorly Bronchoscopy and biopsy substantiated the diagnosis of malignancy the lesion being a squamous-cell carcinoma. The systolic blood pressure was 112 and the diastolic pressure 76. The electrocardiogram (Fig 232 C) was similar to the preceding one except for the presence of incomplete bundle branch block, the deformity in contour of the QRS complexes involving all leads and the duration of the complexes occupying 0 11 0 11 and 0 12 second respectively in the three leads. The patient gradually failed and death occurred three and a half months later

Postmortem examination showed that the heart was markedly hypertrophied weighing 572 gm Rather marked sclerosis of the coronary arteries

and considerable myofibrosis of the left ventricle were present A marked degree of pyelonephritis was disclosed, and there was a squamous-cell carcinoma of the right bronchus with bronchiectasis and formation of abscess

The development of T-wave negativity involving lead I in this case was in all probability dependent on the progression of hypertrophy of the left ventricle consequent to a period of hypertension, in spite of the fact that the blood pressure subsequently dropped to normal Barnes has shown the relationship of T-wave negativity to predominant ventricular strain (in the absence of infarction) and has pointed out that lead I or combined leads I and II is frequently noted in left ventricular hypertrophy The gradual development of bundle-branch block can readily be explained by circulatory interference consequent to the rather marked degree of coronary sclerosis The records of this case extended over a period of four years and four months

Case IV —A man, aged thirty-nine years, came to the clinic May 5, 1925 He was feeling well, but recently his blood pressure was found to be slightly elevated He denied having had any serious diseases, a mild attack

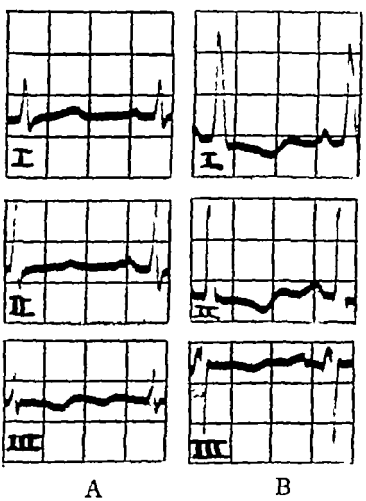


Fig 233 —Successive electrocardiograms A, May 5, 1925, a normal graph B, June 18, 1931, T-wave negativity in leads I and II

of influenza in 1918 and occasional attacks of tonsillitis were the only illnesses recalled

Examination did not reveal abnormalities other than the slight elevation

of blood pressure. The systolic blood pressure averaged 150 and the diastolic 96 Urinalysis, blood counts and the Wassermann reaction of the blood gave negative results An electrocardiogram (Fig 233 A) was negative

A diagnosis was made of mild essential hypertension

The patient was again examined six years later (June 18 1931) and at this time complained of headache in the morning failing vision and increasing dyspnea following undue effort The heart was enlarged the teleoroent genogram revealing the total transverse diameter to be 15 cm Tones were of good quality and the aortic second sound was markedly accentuated The systolic blood pressure was 210 and the diastolic pressure 150 The peripheral arteries were thickened and tortuous. Urinalysis revealed the presence of a moderate amount of albumin The concentration of urea was 66 mg in each 100 c.c. of blood The fundus of the eyes revealed moderate sclerosis of the retinal arteries with mild benign hypertensive retinitis. An electrocardiogram (Fig 233 B) showed well marked negativity of the T waves in leads I and II

The progress of essential hypertension is illustrated in this case, the first examination revealing only slight elevation in blood pressure and no cardiac injury and the next examination, six years later, disclosing marked hypertension and cardiac hypertrophy The electrocardiogram changed from normal to well developed T-wave negativity in leads I and II, evidencing predominant left ventricular strain, the result of hypertension

DEVELOPMENT OF BUNDLE-BRANCH BLOCK

Case V—A man aged thirty five years presented himself for examination April 16 1930 because of increasing dyspnea and palpitation on slight exertion which had its inception eight months previously Slight hemoptysis had occurred on several occasions He had suffered from a rheumatic infection in childhood and had had tonsillitis on several occasions

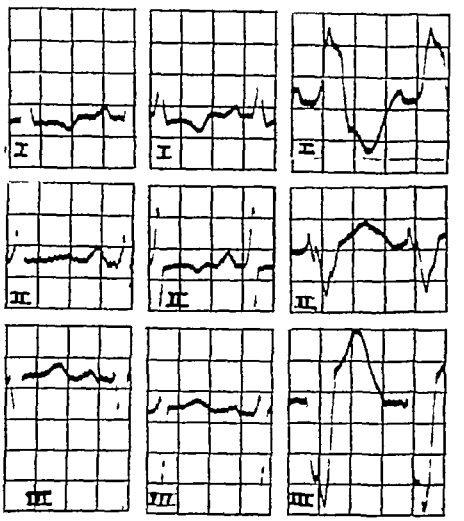
Examination revealed considerable cardiac enlargement and a teleoroentgenogram disclosed the total transverse diameter of the cardiac shadow to be 20 cm. Murmurs were not audible the rhythm was regular and the aortic second sound was frankly accentuated The systolic blood pressure was 172 and the diastolic pressure 140 Urinalysis study of the blood and the Wassermann reaction of the blood gave negative results An electrocardiogram (Fig 234 A) showed T wave negativity in lead I the width of the QRS complexes being within the limits of normal

A diagnosis was made of hypertensive heart disease without congestive failure.

The patient returned for examination nine months later (January 14 1931) with complaints similar to those on his first visit There had been no attacks of pain in the thorax and no edema The physical observations at this time were not particularly different except for the elevation in blood

pressure, the readings now being systolic 210, and diastolic 134 An electrocardiogram (Fig 234, B) now showed T-wave negativity in leads I and II

The patient came again a year later (January 4, 1932) complaining of more severe dyspnea and attacks of retrosternal pain on exertion No re-



A B C

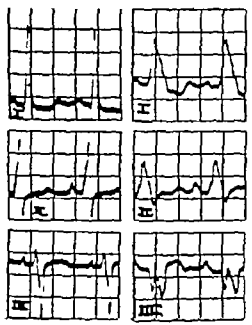
Fig 234.—Successive electrocardiograms A, April 16, 1930, T-wave negativity in lead I B, January 14, 1931, T-wave negativity in leads I and II C, January 4, 1932, complete bundle-branch block.

markable physical changes had taken place, and there was no evidence of congestive failure The systolic blood pressure was 165 and the diastolic pressure 116 The electrocardiogram (Fig 234, C) now revealed complete bundle-branch block.

The first graphic alteration, the T-wave negativity in lead I, was evidently the result of left ventricular hypertrophy consequent to hypertension Nine months later, the T waves were negative in leads I and II The ultimate development of bundle-branch block, in all likelihood, indicated the progress of coronary disease, particularly in view of the occurrence of anginal seizures prior to the last examination

Case VI.—A woman, aged forty-two years, came to the clinic June 19 1930, because nervousness, palpitation and loss of weight had been present for a year Serious illnesses in the past were denied For several years she had been aware of the increase in size of her hands and feet, and her cheek bones were said to be more prominent

At examination the patient presented the typical appearance of acromegaly She had a 'barrel chest with definite diminution in respiratory excursion The total area of cardiac dulness was 16 cm The apex beat was diffuse and heaving and a loud apical systolic murmur was audible transmitted into the axilla There was a trace of dependent edema The systolic blood pressure was 160 and the diastolic pressure 94 Urinalysis revealed a faint trace of albumin The Wassermann reaction of the blood was negative. The basal metabolic rate was +41 per cent An electrocardiogram (Fig 235 A) revealed diphasic T waves in lead I A diagnosis was made of exophthalmic goiter acromegaly and cardiac hypertrophy associated with hypertension



A B

Fig. 235.—Successive electrocardiograms A June 19 1930 diphasic T waves in lead I B October 7 1930 complete bundle branch block.

The patient was treated in the hospital and July 11 1930 subtotal thyroidectomy was performed. She responded well to this procedure her general condition improved and in due time she was permitted to return to her home

The patient returned October 7 1930 her condition generally had improved but she had experienced more dyspnea No marked changes were noted but an electrocardiogram (Fig 235 B) showed the presence of complete bundle branch block.

This case illustrates the influence of two diseases on the myocardium, first the effect of hypertension and later, the influence of hyperthyroidism Both conditions undoubtedly contributed to the progressive myocardial injury The changes described occurred in approximately four months

SUMMARY

Six cases are presented in which the progression of cardiac injury was clearly displayed by serial electrocardiograms The ultimate development of complete heart block was shown in the first two cases The ultimate development of T-wave negativity was shown in the third and fourth cases, and the onset of bundle-branch block in the last two cases

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